Principles and Practice
in Organic Chemistry

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Preface

This laboratory text has the following divisions: (1) an elementary treatment of some fundamental principles such as reaction rate, equilibrium, heat change, and free energy change (Chapter 1); (2) principles of and practice in separation and purification of organic compounds (Chapters 2 to 12 and 45); (3) practice in preparing organic compounds and in studying their chemical behavior (Chapters 13 to 44); and (4) practice in the identification of simple organic compounds (Chapter 46).

In Chapter 1 the discussion of principles is aimed at improving laboratory practice through a better understanding of general relationships, such as (1) influence of temperature and concentration on reaction rate, (2) methods of calculating the heat changes in chemical reactions, and (3) methods of calculating the position of equilibrium in chemical reactions. The student should be able to determine in advance some pertinent facts about a given reaction, in particular, the approximate heat effect and approximate position of equilibrium. It is not expected that the student will at once master the subject matter of this chapter, but at the conclusion of the year's work he should have an appreciation of the importance of these principles in laboratory practice.

The discussion and experiments of Chapters 2 to 12 aim to acquaint the student with the common techniques of separation and purification. After he has gained an understanding of the underlying principles and some experience in the various manipulations, he should be prepared to undertake operations on any scale, large or small. Chromatography is a specialized operation and on this account has been deferred (Chapter 45).

Chapters dealing with organic reactions (Chapters 13 to 44) have three divisions: (1) equations and discussion of general methods of preparation; (2) application of principles to the types of reactions concerned, especially thermochemistry, rates, and methods of purification; and (3) directions for experiments. The experiments are of two types, namely: preparation and properties. The former are listed in the index under "Preparation of," the latter under the respective type of compound.

The inclusion of an abbreviated scheme of qualitative organic analysis (Chapter 46) is believed to be justified as a method of reviewing and correlating the characteristic reactions and solubility relationships of the various classes of organic compounds previously studied. It is recom-

mended that only relatively simple organic compounds be assigned as unknowns.

The directions for preparation have rather extensive notes, in addition to procedure and questions. The notes give additional information, not essential to the experiment itself, which may either explain the reason for a particular procedure or describe the effect of changing conditions, or even give directions for alternative procedures.

Amounts of reactants are given in terms of moles. Sometimes the amount of only one reactant is specified, and the worker must calculate the amounts of other reactants from the equation. Thus the student is made aware of the reacting proportions.

The directions of many experiments are written as general methods of preparation. Although an experiment of this type is described for a particular compound, the use of molal amounts permits easy substitution of other reactants. In general, additional notes pertinent to the change are included.

Tests for completeness of reaction are given whenever feasible. The worker is encouraged to make his own decision in regard to completeness of reaction.

The number of experiments is so large that ordinarily a student cannot be expected to complete all of them in one year. However, different students can work on different preparations in a given chapter or on different modifications of the same preparation, and by exchanging information each can become familiar with a larger variety of experiments than if all the members of the class did the same experiment. The more difficult experiments can be assigned to the more able students.

Preparation experiments vary markedly in difficulty and in the time required. Some can be carried out with simple apparatus, but others may require rather elaborate apparatus. These include fractionating columns, sealed mechanical stirrers, phase separators, Dry Ice reflux condensers, Dry Ice cooling baths, and electrolytic apparatus. Some experiments can be performed in a single laboratory period of three to three and one-half hours, most in two laboratory periods, and some only in three or more periods.

The following experiments require in general about one laboratory period, although in some cases a little more time is needed, as when a final distillation is deferred, or when a solid needs to be dried: Experiment 13–1, Methane; 14–3, 2-Pentene; 16–4, *tert*-Butyl chloride; 21–1, Ethyl acetate; 21–3, *n*-Butyl nitrite; 23–1, Acetyl chloride; 24–1, Acetic anhydride; 24–2, Tartaric anhydride diacetate; 25–1, Acetone; 25–2, Cyclopentanone; 25–4, Acetaldehyde; 28–1, Acetonitrile; 32–1, Nitrobenzene; 33–2, *o*-Aminophenol; 34–2, Methyl orange; 34–3, Para red; 35–1,

Benzyl alcohol; 38–1, *p*-Benzoquinone; 38–2, 1,4-Naphthoquinone; 39–3, Fluorescein; 42–2, *N*-Phenylglycine; 43–2, Glucose pentaacetate.

The following preparations require in general three laboratory periods, but the time is longer in those cases where a long heating time is necessary: Experiment 14–1, Ethylene bromide; 14–2, 2-Butene; 19–5, 3-chloro-2-butanol; 20–2, Propionic acid; 21–2, *n*-Butyl acetate; 22–2, *n*-Butyl ether; 31–1, *p*-Toluenesulfonic acid; 39–2, Malachite green; 40–1, Ethyl *n*-butylacetoacetate; 40–2, Ethyl cyclopropanedicarboxylate; 40–3, Ethyl diacetylsuccinate; 41–1, α-Hydroxy-α-methylbutyric acid; 43–3, Calcium gluconate; 44–2, Indigo. A somewhat longer time is needed for: 15–1, 1-Hexyne; and 18–1 and 18–2 (or 19–4), *n*-Butyl-magnesium bromide and 1-Heptene (or 2-Hexanol).

The longest experiments are 42–3 and 43–1, DL-β-phenylalanine, and α-D-mannose, respectively. The elapsed time for these is about five laboratory periods. However, by the time these are reached the student should have become proficient enough to be working simultaneously on two or more experiments where simple operations are involved, as for example slow addition of a reactant or a long period of heating or stirring.

H. J. LUCAS

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GENERAL DIRECTIONS

1. Plan the work. Read over the experiment before coming to the laboratory, and be prepared to start the experiment on arrival. Time may be saved by obtaining all materials from the stockroom at one time. In those intervals when constant attention is not required during an experiment, as for example when materials are being refluxed or stirred, preparation should be made for the next experiment.

2. Where a choice of experiment is possible, the student should consult other students and the instructor before starting any one experiment so that the largest variety of experiments will be carried out in the laboratory. By watching the work of his neighbors, the student can profit from their experience without doing a large number of extra experiments.

3. A bound laboratory notebook, preferably one ruled vertically, as well as horizontally, is required. Such ruling facilitates the tabulation of results, a desirable feature in keeping notes. Each day's work must be dated, and it is desirable that each page be numbered, so that the book may be indexed and so that references may be made from one part of the book to another. In order that the notes may be a *permanent original* record of the work, they must be made in part while the experiments are in progress and in part as soon as they are finished. They must contain all the original data such as weights, volumes, temperature readings, and pressure readings. Loose sheets of paper are not to be used for making notes. Such sheets are not needed in the laboratory, since calculations can be made in the notebook. In case any data are obtained from others, due acknowledgment must be made.

Never remove a page from the notebook. If a page has been spoiled by mistake, by carelessness, or by an accident, it may be disregarded if such a notation is made. Useful data may be copied onto another page. It is important that the student train himself to keep a clear, accurate, concise and *original* record of the laboratory work. This may not be easy at first but should be possible, especially after a few experiments. The ability to keep such a notebook is valuable in research and in industrial work.

Write on consecutive pages and do not crowd. Starting the experiment on the left-hand page is probably best.

4. In the notebook enter the title of the experiment, a reference to

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the source of directions, and the equations for any reactions that take place during the experiment.

It is not necessary to copy the laboratory directions, but some comments on the experiment should be made. A short statement of the procedure, what phenomenon if any was observed, what difficulty if any arose, and what improvement or change may have been used or could possibly be suggested. Oftentimes a sketch of the apparatus, especially if it is complicated, improves the write-up.

5. *Before starting the experiment* make a table of the reactants and of the products, not only of the principal reaction but also of important side reactions; include in the table the molecular weights of the substances (or atomic weights, in case elements are involved); important physical properties of reactants and products; the amounts of materials taken, in weight or volume; the number of moles of reactants; and the expected amount of product, in grams and in moles. Table 1, a typical table, describes the materials involved in the preparation of ethyl

TABLE 1

PROPERTIES OF COMPOUNDS INVOLVED IN THE PREPARATION OF ETHYL BROMIDE; QUANTITIES AND PERCENTAGE YIELD

Substance	M.W.	Sp. Gr.	M.P., °C.	B.P., °C.	Solubility, g./100 g., in			Quantity Involved		
					Water	Alcohol	Ether	mole	g.	ml.
Potassium bromide	119	3.3	381	.....	79	s. sol.	insol.	1.00	119	....
Sulfuric acid	98	1.832	10	330	misc.	misc.	misc.	1.2	120	65.5
Ethanol	46	0.78	−117	78.3	misc.	misc.	misc.	1.6	75	96
Ethyl ether	74	0.71	−116	34.5	7	misc.	misc.	....	.....	. .
Ethyl bromide	109	1.43	−119	38.4	0.09	misc.	misc.	1.00 *	109 *	76 *
								0.90 †	98.1 †	

* This is the expected amount of product on the basis of a theoretical yield (100%).

† This is the amount actually obtained: yield, 90%.

bromide. The student will find use for many of the data, and for that reason the table should be constructed before the experiment is started. It is not of much value after the experiment has been performed.

6. Understand the object of the experiment. If in doubt, do not hesitate to ask questions of the instructor.

7. Obtain approval of the instructor to go ahead, after the apparatus has been assembled. At the same time, the instructor will approve the use of materials not on the side shelves, by countersigning a stockroom order, which the student should have made out previously.

8. Always determine for yourself the amounts of materials being used by weighing (or by measuring, if the specific gravity is known), and do not take it for granted that the amounts obtained from the stockroom are correct. The student should keep, in a convenient place in the note-

book, the weights of some of the empty vessels, so that the amounts of materials they contain can be ascertained without the necessity of transferring. This is especially desirable if the substance is quite volatile, or unpleasant, or altered on exposure to air.

9. During the experiment record in the notebook the phenomena that are observed. When carrying on distillations or other operations in which conditions are changing, it is desirable to record the readings at frequent intervals. Thus, if temperatures and volumes are recorded simultaneously, the data are available for examination later. In fractional distillation it is especially desirable to keep a complete record of temperature changes (see Experiment 9–1).

In simple distillations the use of previously weighed flasks is advantageous, for then it is necessary only to weigh the receiver plus the distillate. Loss by transfer is avoided. A record of the distillation should be kept, somewhat according to Table 2.

TABLE 2

RECORD OF DISTILLATION

Boiling point, observed, °C.	Up to 37	37.0–40.0
Boiling point, corrected, °C.		37.1–40.1
Weight of receiver, grams	76.5	168.0
Weight of receiver and distillate, grams	79.1	249.0
Weight of distillate, grams	2.6	81.0

10. Keep your mind on your work. Be thinking about the questions while the experiments are being performed, for in many cases the questions serve to emphasize some important feature of the procedure, or to make clear the reason for some particular operation. Develop your powers of observation, and, most important of all, develop the ability to think. The student should understand the reason for each operation he performs, for then he is qualified to proceed to increasingly more difficult experiments.

11. Observe usual precautions to avoid fires. Never heat inflammable liquids in open vessels.

CONSERVATION

In the laboratory, the student should develop the attitude of conservation by guarding against the waste of material objects, such as water, gas, electricity, and chemicals, and of the less tangible but nevertheless more valuable factor, time.

The word conservation represents to a large extent the role which the scientist plays in the industrial world. The improvements in present processes of manufacture, the development of new processes, the utilization of known materials for new purposes, and the discovery and utilization of new substances all result in an economy of either time or materials. In this the scientist takes an important part, either through research or through direct control of industrial processes.

INTRODUCTION

Laboratory work in organic chemistry has a manyfold purpose. The student learns the characteristic properties of the various classes of organic compounds, he learns how to carry out and to control reactions by which these can be prepared, and he learns how to perform carefully and efficiently the many operations involved in the preparation and purification of organic compounds. He should gain a thorough understanding of the underlying principles of reaction control and of purification, and after some time he should acquire the ability to follow intelligently brief outlines of preparations without the elaborate detail that is necessary in the beginning course. Finally, he should have sufficient skill and sufficient confidence to be able to prepare organic compounds with meager directions, or even without any directions.

Chapter 1

CHEMICAL REACTIONS

Reactions differ in many respects. Some proceed rapidly, others slowly. Often reactions proceed until one of the reactants has disappeared. Others come to a stop even when a considerable portion of the original substances remains. In most reactions heat is evolved, although in some heat is absorbed. The rate of the reaction, the extent of the reaction, and the heat effect are the main factors that determine the conditions under which a reaction should be carried out so as to obtain a satisfactory balance of yield of product with economy of time and materials. Therefore it is desirable to know beforehand the magnitude of each of these factors, in order that the proper conditions of concentration and temperature may be maintained.

Moreover, the physical state of the reaction mixture will determine the nature of the procedure. Thus manipulative details vary, depending on whether one handles a gas, a liquid, or a solid. The handling of mixtures, which may be homogeneous or heterogeneous, also may require additional modifications.

The student should understand the principles underlying the methods of procedure followed in the different experiments. He should consult the instructor if in doubt.

SECTION 1.1 REACTION RATES

Organic reactions usually proceed slowly. On this account the methods by which organic reactions can be made to proceed at a satisfactory velocity are of great importance. Speeds of reaction can be controlled by different means, of which the most important are: (1) control of the temperature, (2) use of a catalyst, (3) control of the concentration of one or more reactants.

1.11 Effect of Temperature. The rate of reaction may be increased by raising the temperature, since reactions usually proceed more rapidly when the temperature is raised. The factor by which a 10° rise in temperature on the centigrade scale increases the rate is called the **temperature coefficient** of the reaction rate. The temperature co-

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efficient is generally about three. For a large number of reactions the coefficient is about two, and for some the value may even exceed six (for example, the dehydration of tertiary butyl alcohol). The limit to which the temperature of a reaction mixture can be raised is, of course, limited by practical considerations such as pressure and boiling temperature, as well as by the fact that undesirable side reactions may become important. Usually, however, the boiling point of the mixture limits the temperature. In this case the temperature may be changed by increasing the boiling temperature, either by using a higher boiling solvent or by increasing the pressure. The latter can be accomplished by sealing the reaction mixture in a strong-walled tube, or by the use of an autoclave. A side reaction which has a temperature coefficient greater than that of the desired reaction becomes increasingly more important at the higher temperatures, whereas one having a lower temperature coefficient becomes less important.

1.12 Effect of Catalysts. Most organic reactions can be aided by the addition to the reaction mixture of a suitable catalyst, that is, a substance that accelerates the reaction and yet is recoverable unchanged. The catalysis is called **heterogeneous,** if the added substance is present as a separate phase, and **homogeneous,** if its addition does not increase the number of phases. An important example of heterogeneous catalysis is the reaction of gaseous hydrogen with an unsaturated compound (hydrogenation), carried out in the presence of a solid metal catalyst (nickel, etc.). A good example of homogeneous catalysis is the formation of ethyl acetate from ethyl alcohol and acetic acid in the presence of sulfuric acid. In both cases a pronounced acceleration of the reaction by the catalyst is observed. Since a catalyst often brings about an increase in the reaction rate without the necessity of raising the temperature, a large economy may be effected in time, fuel, and manipulation. Indeed, without catalysts many reactions are impossible, because the elevated temperatures otherwise necessary would cause predominant side reactions.

Although the acceleration of chemical reactions is usually desirable, it is necessary to take into account both the heat effect of the reaction and the potency of the catalyst. When much heat is evolved in a given chemical reaction, it is obvious that careful control is necessary; otherwise, the increase in rate resulting from the rise in temperature may culminate in an explosive reaction. However, if the heat effect is small or if the control of the temperature is adequate, there usually is no reason why the reaction may not be allowed to proceed as rapidly as possible. The importance of understanding the energy relationships in chemical reactions is emphasized in Section 1.3, Heat of Reaction.

Sometimes it is possible to decrease the rate of an undesirable reaction by the presence of a "negative" catalyst. For example, hydroquinone when added to gasoline containing unsaturates usually eliminates gum formation, which otherwise would result from the polymerization of any dienes which might be present.

1.13 Effect of Concentration in Homogeneous Systems. When a reaction takes place between two or more substances, the progress of the reaction depends on the molecules coming in contact with each other. The rate of the reaction, that is, the amount of material transformed in unit time, is directly proportional to the number of collisions per unit time between reacting molecules. The number of collisions, in turn, depends directly on the concentrations. In this way the amount of material transformed in unit time in unit volume, that is, the **rate of reaction,** is proportional to the concentration of each of the reactants. In the reaction of two substances A and B, to give the products C and D:

$$A + B \rightarrow C + D \tag{1-1}$$

the decrease in the concentration of A is proportional to the product of the concentrations of A and B (Equation 1-2), unless the reaction is complicated by the formation of an intermediate substance.

$$\text{Rate of decrease of } (A) = k(A)(B) \tag{1-2}$$

Here (A) and (B) represent the concentrations of A and B, respectively, and k is a constant at any given temperature. It is called the **reaction-rate constant.** Since the rate depends on the first power of the concentration of each of the reactants, the reaction is said to be **first order** with respect to both A and B. It is called a **second-order** reaction since it is first order with respect to two substances.

The rate with which two substances A and B react with each other to form C and D, that is, the amounts of A and B that disappear in unit time in unit volume will be greatest initially, provided neither one reacts with the products and provided also that other conditions remain unchanged. The reason for this is that the concentrations of the reactants are the greatest immediately after mixing, before any reaction has taken place. As reaction proceeds, with the formation of the products, the concentrations of A and B become continuously smaller. In case there is only one phase and its volume remains essentially unchanged, as would be true if neither C nor D separates as a second phase, the concentrations of A and B at any given time t, subsequent to their mixing, will be proportional to the amounts remaining unreacted at that time. The rate of reaction therefore will be less at time t than it was initially. The extent of the decrease in the reaction rate will depend on

the decrease in the concentrations of both A and B and may be ascertained roughly through a calculation of the reaction rate by means of Equation 1–2. This is an approximate result only, for the presence of the products may alter the nature of the reaction mixture.

It is instructive to show in a roughly quantitative fashion how the rate of reaction decreases as the reaction proceeds. If the concentration of each reactant is expressed as a **mole fraction** (ratio of number of molecules of a reactant to total number of molecules present), it is clear that, when equal molal amounts of the reactants are taken, the initial rate is given by Equation 1–3, and, when one half of A and B have reacted, the rate is given by Equation 1–4.

$$\text{Rate}_i = k(0.5)(0.5) = 0.25k \tag{1-3}$$

$$\text{Rate}_{\frac{1}{2}} = k(0.25)(0.25) = 0.0625k \tag{1-4}$$

From this it may be seen that at the halfway point the rate is only one fourth of the initial rate. Likewise, when the reaction has proceeded three fourths of the way to completion, the rate is $0.0156k$, that is, only $\frac{1}{16}$ of the initial rate. The rate drops rapidly as the reaction continues beyond this point. This calculation is made on the assumption that no second phase separates.

When two molecules of the substance A react with each other to give the products C and D, according to Equation 1–5,

$$A + A \rightarrow C + D \tag{1-5}$$

the rate of decrease of (A) depends on the frequency of collision between molecules of A (Equation 1–6) in a manner similar to the way the rate of afore-mentioned reaction of A with B depends on the frequency of collision of the molecules of A with those of B.

$$\text{Rate of decrease of } (A) = k(A)(A) = k(A)^2 \tag{1-6}$$

Here the (B) of Equation 1–2 is replaced by (A). The rate drops off as the reaction proceeds in the same manner as for the reaction of A with B. This type of reaction is **second order** with respect to A.

If the compound A decomposes by itself, the rate of decrease of (A) depends only on the concentration of A, as shown in Equation 1–7.

$$\text{Rate of decrease of } (A) = k(A) \tag{1-7}$$

This type of reaction is **first order** with respect to A and is called a **first-order** reaction. The rate drops off much more gradually as the reaction proceeds than does that of a second-order reaction.

The influence of concentration on reaction rate is of great importance in organic laboratory work. If two substances react too rapidly by themselves, the reaction can be controlled by regulation of the concentrations. Thus the concentrations of both reactants may be lowered by the addition of a suitable solvent, or the concentration of one reactant may be kept low by adding it slowly to the other reactant. By either procedure the reaction can be kept under control. The course of side reactions also is greatly affected by concentration. If the principal reaction is first order and the side reaction is second order, the side reaction can be greatly diminished by dilution. Dilution to half the original concentration halves the rate of the principal first-order reaction but quarters the rate of the second-order side reaction. On the other hand, if the side reaction is first order and the principal reaction is second order, the side reaction can be diminished relatively by increasing the concentration. The choice of the procedure depends on many other factors such as the solubilities and the physical states of the reactants and products. Another factor that must be considered also is the problem of carrying the reaction to completion.

1.14   Effect of Increasing the Concentration of One Reactant. Often it is desirable to have a reaction proceed essentially to completion with respect to a reactant, especially when this reactant is expensive, is difficult to prepare, or is difficult to separate from the product. It is essential then to keep the velocity of conversion of this reactant reasonably high while its concentration drops. This may be accomplished by adding an excess of the other reactant or reactants.

The value of an excess reactant is shown by the use of 100% excess of B in the reaction of A and B. The initial rate is $0.22k$ (Equation 1–8), and, by the time three fourths of A have reacted, the rate is $0.0347k$ (Equation 1–9) where the concentrations are given as mole fractions.

$$\text{Rate}_i = k(0.33)(0.67) = 0.22k \qquad (1\text{–}8)$$

$$\text{Rate}_{¾} = k(0.33 - 0.33 \times ¾)(0.67 - 0.33 \times ¾) = 0.0347k \qquad (1\text{–}9)$$

Starting with a total of 1 mole of A, the actual initial velocity of conversion of A, expressed as moles reacting per unit time, is $3 \times 0.22k$ (Equation 1–8) or $0.67k$ when 2 moles of B are taken at the beginning, but it is $2 \times 0.25k$ (Equation 1–3) or $0.50k$, when only 1 mole of B is so taken. The actual velocity of conversion of A when three quarters of A have reacted is $3 \times 0.035k$ (Equation 1–9) or $0.105k$, when 2 moles of B are taken initially, and $2 \times 0.0156k$ or $0.031k$, when only 1 mole of B is so taken. Thus, when there is a 100% excess of B at the start, the initial velocity of conversion of A is somewhat greater than when there

is no excess of B, and at the three-quarters point it is three times greater.

The effect of excess of one reactant becomes even more important as the reaction nears completion beyond this point. With an excess of one reactant, therefore, the reaction may be driven to completion with respect to the other substance in a shorter length of time than when equal molal amounts are taken.

These comparisons have been made on the basis of two assumptions. One assumption is that C and D, the products of the reaction, remain in solution. If one of the products separates as a second phase (gas, liquid, or solid), the concentrations of A and B will not decrease so rapidly as under the assumed conditions, and the rate will not drop off so rapidly as pointed out previously for a homogeneous reaction. Another assumption is that the reactivities of A and B are proportional to their concentrations. Such an assumption is only an approximation, which holds moderately well for dilute solutions in general and for concentrated as well as dilute solutions of nonpolar compounds in nonpolar solvents.

1.15   Reactions in Heterogeneous Systems.   The foregoing discussion is concerned with homogeneous systems only. Often reactions are carried out in two-phase systems, for example, those consisting of a gas and a liquid, a gas and a solid, two liquids, a liquid and a solid, or two solids. Sometimes they are carried out in even more complicated systems. The problem is to obtain a reaction between two substances not in the same phase. Reaction can take place only at the point where the substances touch each other. One way of increasing the reaction rate is to increase the contact area. This can be accomplished by bringing the different phases into as intimate contact as possible, so as to make the interface a maximum. For this it is necessary that the phases be in a high state of subdivision and of agitation. If one phase is a liquid, then vigorous agitation will give good contact, whether the other phase is gas, liquid, or solid. If one phase is a solid, it should be in a fine state of subdivision. If both are solid, reaction will be exceedingly slow. Agitation may be manual, that is, by hand, or mechanical, that is, by means of a stirrer or a shaking machine.

Another method of increasing the reaction rate of a heterogeneous system is to convert it to a homogeneous system by the addition of a suitable solvent (see Chapter 2 on Solubility). This permits collision between molecules of the reactants without the necessity of agitation. Oftentimes it is not desirable to add sufficient solvent to bring all the reactants into solution, since, if this is done, the concentrations of both reactants and, hence, the reaction rate, drop rapidly as the reaction

proceeds. On the other hand, if the amount of solvent is insufficient to dissolve the reactants completely, the concentration of each in the solution remains essentially unchanged at its maximum value until after it has dissolved entirely. However, since the rate with which solution takes place is dependent on the interfacial area, the system should be treated as heterogeneous, and on this account agitation is desirable. Fortunately there usually is some solubility in a liquid phase of the other phase, whether it be gaseous, liquid, or solid, and hence an additional solvent is not always necessary when one of the reactants is a liquid.

SECTION 1.2 EQUILIBRIUM

It was pointed out previously that in some cases reaction proceeds only part way to completion. The reason is that the reverse reaction comes into play. However, the percentage of organic reactions that proceed to a measurable equilibrium under ordinary conditions is not very great, although many examples of this type of reaction are known. In many cases the equilibrium lies so far to one side that the reverse reaction is negligible. For the discussion here the expression *reversible* will be limited to those systems in which the reversibility is extensive enough to be demonstrated experimentally.

1.21 The Equilibrium Constant. When the rates of the forward and reverse reactions in a homogeneous chemical system are comparable, a measurable equilibrium is set up, as shown by Equation 1–10.

$$. \quad \underset{\text{acetic acid}}{CH_3COOH} + \underset{\text{ethyl alcohol}}{HOC_2H_5} \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} \underset{\text{ethyl acetate}}{CH_3COOC_2H_5} + \underset{\text{water}}{H_2O} \qquad (1\text{–}10)$$
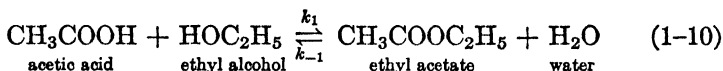
The rate of formation of ethyl acetate and water is given by Equation 1–11, and the rate of disappearance of the same substances is given by Equation 1–12.

$$Rate_{\text{formation}} = k_1 \text{ (acid) (alcohol)} \qquad (1\text{–}11)$$

$$Rate_{\text{disappearance}} = k_{-1} \text{ (acetate) (water)} \qquad (1\text{–}12)$$

In these expressions k_1 and k_{-1} are the reaction-rate constants for the forward and reverse reactions, respectively, and the expressions in parentheses represent concentrations. The equilibrium, where the rate of disappearance of the ester and water equal the rate of their formation, is expressed by Equations 1–13 and 1–14:

$$k_1 \text{ (acid) (alcohol)} = k_{-1} \text{ (acetate) (water)} \qquad (1\text{–}13)$$

$$k_1/k_{-1} = \text{(acetate) (water)/(acid) (alcohol)} = K \qquad (1\text{–}14)$$

Here K the equilibrium constant can be expressed as a ratio of the specific reaction rate constants k_1/k_{-1} or in terms of the concentrations of all of the reacting substances. The equilibrium constant K at 25° in the ethyl acetate reaction remains essentially constant at 4 over a wide range in the concentrations of the four components. This means that, when equimolal amounts of the acid and alcohol are taken, approximately two thirds of the initial compounds react by the time equilibrium is reached. From a thermodynamic point of view an equilibrium constant can be calculated for all chemical reactions. The method of calculating the equilibrium constant from thermodynamic data is given in Section 1.4, Free Energy.

Since the reaction rate drops greatly as a reaction mixture approaches equilibrium, it is not always practical to wait until equilibrium is reached before removing the product. An equilibrium reaction may be driven to practical completion by changing the concentration of one or more of the reactants, by removing a product, or sometimes by changing the temperature.

1.22 Effect of Concentration. It has been shown already in the irreversible reaction of A with B that the rate of formation of the products C and D at the stage where 75% of A has reacted is increased by having B in excess. When the system is reversible, C and D can react to form A and B. Since C and D are formed in equal molal amounts, an excess of B has no effect on the reverse rate other than to retard it somewhat owing to dilution. Thus the presence of excess of B will cause the equilibrium to shift towards the right, owing to the fact that the forward reaction is accelerated, whereas the reverse reaction is retarded slightly.

By the use of Equation 1–14 it is possible to calculate the mole fractions of the reactants and products at equilibrium, on the basis that the equilibrium constant K is 4. Thus, when equimolar amounts of acid and alcohol are taken initially, the respective initial and equilibrium concentrations, expressed in mole fractions, are as follows: (Acid) = 0.50 and 0.17; (alcohol) = 0.50 and 0.17; (ester) = 0.00 and 0.33; (water) = 0.00 and 0.33. Thus two thirds of the original acid and alcohol have reacted. On the other hand, if the initial concentration of the acid is twice that of the alcohol, the respective initial and equilibrium concentrations are: (Acid) = 0.67 and 0.39; (alcohol) = 0.33 and 0.05; (ester) = 0.00 and 0.28; (water) = 0.00 and 0.28. Thus in the latter case five sixths of the initial alcohol has been converted to the acetate, whereas in the former only two thirds has been converted. Naturally, the fraction of the acid converted is less in the second instance.

In an equilibrium system involving two reactants, therefore, one of the reactants may be caused to react more or less completely by the use of an excess of the other reactant. In the example just cited, it is evident that, on increasing the mole fraction of acid even more, that is, above 0.67, an even greater percentage of alcohol will be converted at equilibrium. However, from a practical point of view, in this case there is little to be gained from such a procedure because the cost is increased and because the recovery of the desired product from the reaction mixture is rendered more difficult by the needlessly large excess of acid. This complication is such a common one that in many cases little is gained by the use of a large excess of one reactant.

1.23 Effect of Temperature on the Position of Equilibrium. Since a reaction rate is increased by raising the temperature, it is evident that both the forward and reverse reactions are accelerated by a rise in temperature. Thus the equilibrium conditions can be attained more rapidly by heating. However, the concentrations of the components of any one equilibrium system are, in general, different at the two temperatures, because usually reactions are not affected equally by a temperature change. Thus the rate constant of the reverse reaction may increase (or decrease) faster than that of the forward reaction. The result is a shift in the position of equilibrium. The direction and extent of this shift are discussed in Section 1.3, Heat of Reaction.

1.24 Effect of Catalysts on Equilibria. In general, catalysts have no effect on equilibria. When a catalyst is added for the purpose of increasing the rate of the forward reaction, the rate of the reverse reaction is increased also; otherwise there would be a shift in the equilibrium.

1.25 Effect of Removing a Product. The most satisfactory method of obtaining good yields of products from reactions which reach a measurable equilibrium involves the removal of at least one of the products from the reaction mixture. Since the rate of the reverse reaction is proportional to the concentration of each of the products, a decrease in the concentration of one of them results in a decrease in the rate of the reverse reaction. However, the rate of the forward reaction is not diminished since this depends only on the concentrations of the original reactants. As a result, the reaction proceeds towards completion. The removal of one of the products of a reaction may result spontaneously by the formation of a separate gaseous, liquid, or solid phase, or it may be brought about mechanically, as by distillation, or it may be done chemically by rendering the product unreactive through combination with some other substance.

1.26 Predicting Approximate Equilibrium Constants. It is evident from these discussions that the procedure to be adopted in

laboratory preparations depends on whether the products result from irreversible or reversible reactions. It would be convenient to know, previous to undertaking an experiment, whether or not the reaction theoretically would proceed to completion, provided there are no side reactions. This information can be obtained from ΔF, the free energy change of the reaction as discussed in Section 1.4, Free Energy.

SECTION 1.3   HEAT OF REACTION

Heat is evolved in an **exothermic** reaction, and is absorbed in an **endothermic** reaction. The **heat of the reaction** is the heat that would be given off during a reaction if the initial and final states were at the same temperature. It arises from a change ΔH in the **heat content** H of the system during the reaction. Thus, when the sum of the heat contents of the products of a reaction is *less* than the sum of the heat contents of the reactants, the reaction is exothermic, because heat is given off. Therefore, the change in the heat content of the system, $H_{products} - H_{reactants}$, ordinarily indicated as ΔH, is negative. Conversely, when the sum of the heat contents of the products of a reaction is *greater* than the sum of the heat contents of the reactants, the reaction is endothermic because heat is absorbed. In this case ΔH is positive.

The heat content of a substance may be expressed in calories or kilocalories per mole. For elements it is arbitrarily taken as zero in some chosen standard state, usually 25°, and 1 atmosphere. The heat content of a compound in some specified state is then the ΔH that accompanies the formation of 1 mole of the compound from its elements, in their standard states. The term **heat of formation** Q is sometimes used in this connection. When carried out at constant pressure in such a way that no work other than pressure–volume work has been done, it is the heat evolved in the formation of 1 mole of the compound from its elements at 25° and 1 atmosphere pressure, that is, $-\Delta H_{298}$. The use of these units is illustrated in the formation of carbon dioxide from graphite and gaseous oxygen, at 1 atmosphere and 25°:

$$C(s) + O_2(g) \rightarrow CO_2(g) + 94.030 \text{ kcal.} \qquad (1\text{--}15)$$
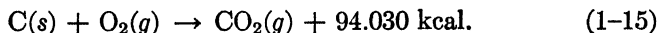
Here heat is given off, and the reaction is exothermic. The heat of the reaction is +94.0 kcal., and ΔH_{298} is −94.0 kcal. The heat content of carbon dioxide is −94.0 kcal., and its heat of formation Q is +94.0 kcal.

1.31   Effect of ΔH on the Progress of Reactions. Heat changes in reactions may add complications to laboratory procedure. When the reaction is endothermic, heat should be supplied to the system; otherwise

the temperature drops, and the reaction rate decreases. However, reactions seldom are endothermic and are never strongly endothermic. This will be evident from the discussion on free energy change, in Section 1.4.

When the reaction is exothermic, the temperature of the reaction mixture rises. The rise in temperature causes an increased reaction rate. This is an advantage, for when the reaction is exothermic it is unnecessary to apply external heat. However, care must be taken that the increased reaction rate in turn does not lead to such a rapid evolution of heat and thus to such a marked increase in temperature that the reaction gets out of control. Special precautions must be taken when the reaction is exothermic, especially if the amount of heat evolved is large. This will be the case if $-\Delta H$ is large or if the amount of reaction mixture is large.

Several procedures are available for controlling an exothermic reaction. It is dangerous in any case to add all the reactants at the beginning, for the temperature of the mixture may rise, even when a cooling bath is used. It is best to add one of the reactants slowly to the other, either allowing the heat to dissipate, or removing the heat by cooling during the addition. The cooling should not be so intense as to slow the reaction excessively; otherwise too large an amount of unreacted material will be present. This then would be essentially the equivalent of having added all of the reactants initially. For this reason *the temperature of the reaction mixture should be one at which the added material reacts rapidly and yet under control.* Cooling may be accomplished by immersing the reaction flask in water at different temperatures, in ice, in a freezing mixture of ice and salt, or, should a very low temperature be desired, in a bath cooled by Dry Ice. Agitation of the reaction mixture is desirable during cooling; otherwise the central part of the system may be much warmer than the outer part. An excellent method of controlling the temperature is the use of a volatile solvent which boils out of the reaction mixture and is continually returned by means of a condenser. The advantage of this procedure lies in maintaining a uniform and constant temperature.

If the approximate heat of the reaction is known, the heat effect that accompanies the reaction can be predicted. The necessary control conditions can be anticipated and the apparatus designed accordingly. In case an anticipated high heat evolution does not materialize, it is evident that the rate of the reaction is too low. The rate should be raised, in accordance with the principles discussed previously, before the amounts of reacting substances present reach the danger stage.

1.32   Effect of ΔH on the Equilibrium Constant. In a reversible reaction the rate of change in the equilibrium constant K with temperature is dependent on the value of ΔH, although the actual value of the constant is not determined by ΔH. In the simple system represented by Equation 1–16,

$$A + B \rightleftharpoons C + D + \text{heat} \tag{1-16}$$

heat acts as one of the products. According to the principle of Le Chatelier, which states that, when a stress is applied to a system at equilibrium, the system changes so as to relieve the strain, application of heat to the system under discussion causes some reversal of the reaction. The reason is that heat is absorbed by the reverse reaction, and in this way part of the "strain" resulting from the application of heat is relieved. When ΔH is negative, as in this case, the rate of the forward reaction is increased less than the rate of the reverse reaction by a rise in temperature. Thus the reverse reaction becomes relatively more prominent at the higher temperature, and the equilibrium constant has a smaller value than at the lower temperature. If two separate equilibria are compared, the shift in the constant with a given rise in temperature would be expected to be more pronounced in the case of the equilibrium for which ΔH has the greater numerical value.

The quantitative relationship between ΔH and the equilibrium constant is given by Equation 1–17, the integrated van't Hoff equation.

$$\log_{10} K_2/K_1 = \Delta H(T_2 - T_1)/2.303RT_1T_2$$
$$= \Delta H(T_2 - T_1)/4.58T_1T_2 \tag{1-17}$$

Here K_1 and K_2 are the equilibrium constants at the absolute temperatures T_1 and T_2; ΔH is the change in the heat content, expressed in *calories* per mole; and R is the universal gas constant, 1.99 cal. per mole. This equation is not rigorous because ΔH changes with the temperature. It may be used, nevertheless, for the purpose of predicting the approximate shift in the equilibrium with change in the temperature, if the equilibrium constant and the value of ΔH at some one temperature are known.

1.33   Calculation of ΔH from Heats of Formation and Heats of Combustion. It is important to know the value of ΔH for a given reaction, in connection with control of temperature and equilibrium. The values of ΔH for many reactions have been determined experimentally by: (1) direct calorimetric measurement, or (2) calculation from the change in the equilibrium constant with change in temperature (Equation 1–17). Also, ΔH values may be calculated from: (3) previously determined heats of formation of reactants and products, or (4)

bond energy values. For only a relatively few reactions has ΔH been determined experimentally by methods 1 or 2, owing in part to experimental difficulties and in part to other complications such as side reactions. On the other hand, methods 3 and 4 are of general application. In method 3 a table of heats of formation of organic and inorganic compounds enables one to calculate the heats of reaction in which these compounds are concerned. In method 4 a table of bond energies of different types of bonds enables one to calculate approximately the heats of reactions in which the different bonds are involved (see Bond Energies, 1.35).

Heats of formation of organic compounds seldom are obtained by direct measurement, since their formation directly from the elements in general is not possible. Usually the heat of formation of an organic compound is calculated from its heat of combustion. The general procedure is to burn the substance and thus determine the heat of combustion. Since the heats of formation of the products, usually carbon dioxide and water, are accurately known by direct measurement, the heat of formation of the organic substance is then easily calculated as the difference between its heat of combustion and the heats of formation of the oxidation products. For example, the heat of combustion of 1 mole of gaseous methane CH_4 to 1 mole of gaseous carbon dioxide and 2 moles of liquid water is 212.79 kcal. (Equation 1–18):

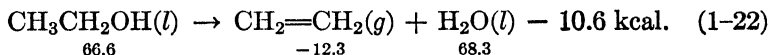$$CH_4(g) + 2O_2(g) \rightarrow CO_2(g) + 2H_2O(l) + 212.79 \text{ kcal.} \quad (1\text{--}18)$$

$$C(s) + O_2(g) \rightarrow CO_2(g) + 94.030 \text{ kcal.} \quad (1\text{--}19)$$

$$H_2(g) + \tfrac{1}{2}O_2(g)^{\cdot} \rightarrow H_2O(l) + 68.313 \text{ kcal.} \quad (1\text{--}20)$$

$$C(s) + 2H_2(g) \rightarrow CH_4(g) + 17.87 \text{ kcal.} \quad (1\text{--}21)$$
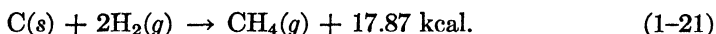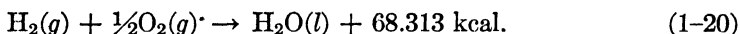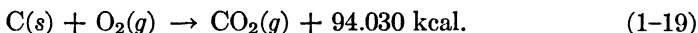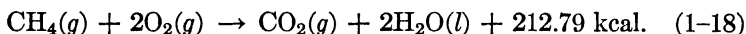
Since the heat of formation of carbon dioxide is 94.030 kcal. (Equation 1–19) and of water is 68.313 kcal. (Equation 1–20) the heat of formation of the combustion products of 1 mole of methane is 230.66 kcal. Thus ΔH_{298} of formation of methane is $212.79 - 230.66$ or -17.87 kcal. (Equation 1–21), and the heat of formation Q of methane is $+17.87$ kcal. It must be kept in mind that the heat of a reaction has the opposite sign from ΔH. When the heat of the reaction is positive, heat is given off, and the heat content of the products is then less than that of the reactants.

The use of heats of formation in the calculation of ΔH is illustrated in Equation 1–22, the decomposition of ethyl alcohol into ethylene and water at 25°. Actually, no reaction takes place at this temperature, but ΔH may be calculated, since the heats of formation at 25° are known. All three values are calculated from heats of combustion. The heats of formation Q are placed below the respective formulas:

$$CH_3CH_2OH(l) \rightarrow CH_2{=}CH_2(g) + H_2O(l) - 10.6 \text{ kcal.} \quad (1\text{--}22)$$
$$\underset{66.6}{} \quad \underset{-12.3}{\phantom{CH_2{=}CH_2(g)}} \quad \underset{68.3}{}$$

Since in the formation of the reactant from the elements the heat that has been evolved, namely, 66.6 kcal., exceeds by 10.6 kcal. the heat evolved in the formation of the products from the elements, namely, 56.0 kcal., 10.6 kcal. must be absorbed in the reaction. Therefore ΔH_{298} is $+10.6$ kcal.

Heats of combustion may be used instead of heats of formation for calculating ΔH. This method is preferred since it is simpler. Usually heats of formation are obtained from heats of combustion. Two examples are cited to illustrate the use of heats of combustion. In the equation the values at $25°$ are written below the formulas. The first example is the hypothetical dehydration of ethyl alcohol

$$CH_2CH_2OH(l) \rightarrow CH_2{=}CH_2(g) + HOH(l) - 10.6 \text{ kcal.} \quad (1\text{--}23)$$
$$\underset{326.7}{} \quad \underset{337.3}{\phantom{CH_2{=}CH_2(g)}} \quad \underset{0}{}$$
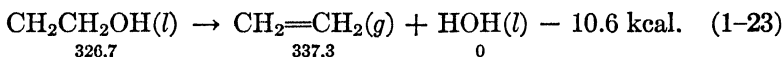
The heat content of the products exceeds the heat content of the reactant by 10.6 kcal., since the sum of the heats of combustion of the former, namely, 337.3 kcal., exceeds the heat of combustion of the latter, namely, 326.7 kcal. by this amount. Therefore, 10.6 kcal. must be absorbed in this reaction.
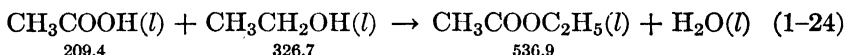
The second example is the reaction of acetic acid with ethyl alcohol to form ethyl acetate and water (Equation 1–24). Heats of combustion are written below the formulas.

$$CH_3COOH(l) + CH_3CH_2OH(l) \rightarrow CH_3COOC_2H_5(l) + H_2O(l) \quad (1\text{--}24)$$
$$\underset{209.4}{} \quad \underset{326.7}{} \quad \underset{536.9}{}$$

By the same method of calculation, the reaction here is slightly endothermic, and ΔH is $+0.8$ kcal. In this case the result should not be regarded as very accurate, since it is a small difference between large numbers. However, the conclusion can be drawn that ΔH has a small numerical value in this reaction.

1.34 Bond Energy. An approximate value for ΔH may be calculated from bond energies. Bond energy is defined as the heat that is liberated, that is, $-\Delta H$, when two free atoms combine to form a bond between the two atoms in a gaseous molecule. The bond energy is expressed in terms of kilocalories per mole. It is also the heat that must be absorbed, that is, ΔH, in order to break a bond in a gaseous molecule. In more complicated systems, the ΔH of the reaction may be calculated as the difference between the total of the bond energies of the reactants and that of the products. If the total of the bond energies of the products is larger than that of the reactants, heat is evolved, and ΔH is negative; conversely, if it is smaller, heat is absorbed, and ΔH is positive. *Only*

for gaseous reactions, that is, where reactants and products are gases, can the ΔH values be calculated from bond-energy values alone. However, the method can be extended to condensed systems by taking account of the heats of transition involved in conversion to the gaseous state. (See Table 8-1 for heats of vaporization.)

In Table 1-1 are listed bond energy values for most of the common bonds. These values have been calculated from a variety of experimental data, as, for example, experimentally determined ΔH values, heats of combustion, and spectroscopic data available from absorption spectra and Raman spectra. The bond energies tabulated are averages over several compounds and, except for the carbonyl and cyanide groups, are uncorrected for structural effects. Therefore their use in calculation of ΔH yields only approximate results. When inorganic acids, bases, and salts enter the reaction, their heats of formation must enter the calculation also.

TABLE 1-1

SOME COMMON BOND-ENERGY VALUES

in kcal. per mole

Pauling, 1940

Bond	Bond Energy	Bond	Bond Energy	Bond	Bond Energy
H—H	103.4	N—N	20.0	C=C	100
H—C	87.3	N—O	34.0 *	C=N	94
H—N	83.7	N—S		C=O	142 †
H—O	110.2	N—F	68.8	C=O	149 ‡
H—S	87.5	N—Cl	38.4	C=O	152 §
H—F	147.5	N—Br	33 *	C=S	103
H—Cl	102.7				
H—Br	87.3	O—O	34.9	N=N	46 ‖
H—I	71.4	O—S	72.4 *	N=O	68 ‖
		O—F	58.6	O=O	118 ¶
C—C	58.6	O—Cl	49.3	O=S	120§§
C—N	48.6	O—Br	49.8	S=S	101§§
C—O	70.0	S—S	63.8		
C—S	54.5			C≡C	123
C—F	107.0	F—F	63.5	C≡N	144 **
C—Cl	66.5	Cl—Cl	57.8	C≡N	150 ††
C—Br	54.0	Br—Br	46.1		
C—I	45.5	I—I	36.2	N≡N	170 ‡‡

* Predicted.
† Formaldehyde.
‡ Other aldehydes.
§ All other carbonyl groups.
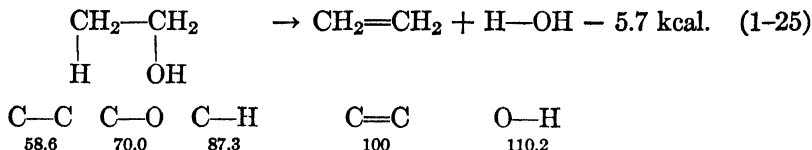‖ Rough approximation, by L. and P.

¶ The oxygen molecule, O_2.
** Hydrogen cyanide.
†† Nitriles.
‡‡ The normal nitrogen molecule, N_2.
§§ K. Pitzer, 1948.

1.35   Calculation of ΔH from Bond Energies.   The use of bond energies in the calculation of the ΔH of reactions is illustrated by the hypothetical gas-phase dehydration of ethyl alcohol at room temperature:

$$\begin{array}{c} \text{CH}_2\text{---CH}_2 \\ | \quad\quad | \\ \text{H} \quad\ \text{OH} \end{array} \quad \rightarrow \text{CH}_2{=}\text{CH}_2 + \text{H---OH} - 5.7 \text{ kcal.} \quad (1\text{--}25)$$

$$\underset{58.6}{\text{C---C}} \quad \underset{70.0}{\text{C---O}} \quad \underset{87.3}{\text{C---H}} \qquad \underset{100}{\text{C}{=}\text{C}} \qquad \underset{110.2}{\text{O---H}}$$

The three bonds of alcohol that suffer change are on the left, and the three new bonds that are formed, a double bond being counted as two bonds, are on the right. The former total 215.9 kcal.; the latter total 210.2 kcal.   Going from the higher to the lower bond-energy values requires the absorption of energy. Therefore the gas-phase reaction is endothermic, and ΔH is $+5.7$ kcal.

When bond energies are used for calculating ΔH, only the bonds broken and the new bonds formed need be considered. However, the number of bonds formed must equal the number broken. For this purpose a double bond counts as two bonds, and a triple bond as three.

In order to make a comparison with the value obtained in Equation 1–23, by heats of combustion, heats of vaporization of alcohol and water must be considered. This is done by adding to the value obtained in Equation 1–25 the molal heat of vaporization of alcohol, namely, 9.4 kcal., and subtracting that of water, namely, 9.7 kcal. Therefore, the estimated ΔH for the reaction in the liquid state, from bond energies, is $+5.4$ kcal.   The discrepancy of 5.2 kcal. between this value and that from heats of combustion (Equation 1–23) is due mainly to the fact that bond energies are average values.

Calculation of ΔH from bond-energy values may lead to results with large percentage error, not only when the ΔH value is numerically small, but even in other cases, if certain complicating factors are not taken into account. The most important of these are the molal heats of vaporization for conversion to the gaseous state, the variation in the value of a given bond energy resulting from structural changes in molecules, and the resonance energies resulting from certain combinations of bonds in molecules. Molal heats of vaporization of many compounds (see Table 8–1) are seen to vary from 5 to 10 kcal. The variation in a given bond energy among different compounds sometimes may be considerable, as shown by the variation in the values for the carbonyl ($\text{C}{=}\text{O}$) bond (Table 1–1), from 142 to 152. However, probably no other bond shows such a wide range in bond energy as this one. The structural differences
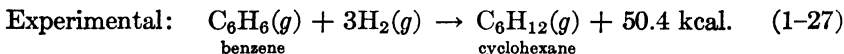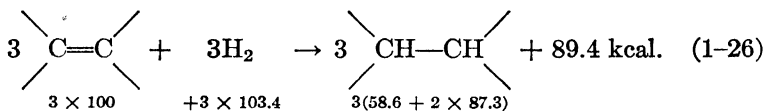
that are responsible for this variation probably cause similar but smaller effects in other bond types.

1.36 Resonance Energy. The most serious complication in the estimation of ΔH from bond-energy values is resonance. This is the stabilizing effect that is present in any molecular system for which two or more electronic structures can be written. For example, two electronic structures, I and II, can be written for benzene C_6H_6:
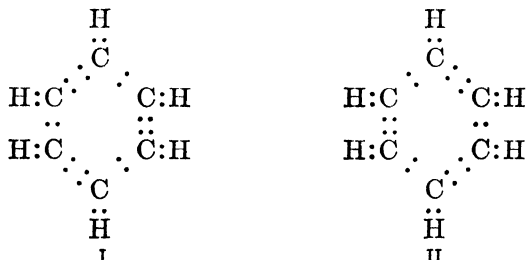
Although these two formulas are equivalent, nevertheless they represent two different arrangements of the electrons in the molecule. Merely because of this fact the molecule is much more stable than it would be if it could be represented by I or II alone. This is shown by the discrepancy between the calculated ΔH of hydrogenation of three double bonds, namely, -89.4 kcal., as calculated from bond energies alone (Equation 1–26) and the experimentally determined ΔH of hydrogenation of benzene, namely, -50.4 kcal. (Equation 1–27).

Calculated:

$$3 \ \diagdown\text{C}\!\!=\!\!\text{C}\diagup \ + \ 3\text{H}_2 \ \rightarrow \ 3 \ \diagdown\text{CH}\!\!-\!\!\text{CH}\diagup \ + \ 89.4 \text{ kcal.} \qquad (1\text{--}26)$$

$$\underset{3 \times 100}{} \quad \underset{+3 \times 103.4}{} \quad \underset{3(58.6 + 2 \times 87.3)}{}$$

Experimental: $\quad C_6H_6(g) + 3H_2(g) \ \rightarrow \ C_6H_{12}(g) + 50.4 \text{ kcal.} \qquad (1\text{--}27)$

$$\underset{\text{benzene}}{} \qquad\qquad\qquad \underset{\text{cyclohexane}}{}$$

The difference between the calculated and experimental values, namely, -39 kcal., represents the ΔH of stabilization, that is, the stabilizing effect of three conjugated double bonds in benzene. The increased stability resulting from the resonance structure is called the resonance energy and in this case is 39 kcal. Any molecule or ion for which two or more electronic configurations may be written has a higher heat of formation than would be predicted in the absence of resonance. The more similar the different structures are, the greater is the stabilization effect. This stabilization, the resonance energy, appears as a decrease in the heat content and as an increase in Q, the heat of formation from the elements.

When a calculation of ΔH for a reaction is made from the bond-energy values, the resonance correction is made by adding the resonance energies of the reactants and subtracting the resonance energies of the products. Table 1-2 gives the resonance energies for a number of compounds.

TABLE 1-2

SOME EMPIRICAL RESONANCE-ENERGY VALUES

Pauling, 1940

Compound	Group	Resonance Energy
Carbon monoxide	C≡O	58
Carbon dioxide	O═C═O	33
Carbonate ion	CO_3^-	42
Carbon oxysulfide	O═C═S	20
Carbon disulfide	S═C═S	11
Nitric acid	HO—NO_2	25
Nitrate ion	NO_3^-	45
Alkyl isocyanates	R—N═C═O	7
Aliphatic acids	R—(C═O)—OH	28
Esters	R—(C═O)—OR'	24
Carboxylate ions	R—(C═O)—O⁻	36
Dialkyl carbonates	RO—(C═O)—OR	42
Amides	R—(C═O)—NH_2	21
Urea	H_2N—(C═O)—NH_2	37
Guanidine	H_2N—(C═NH)—NH_2	47
Butadiene	C_4H_6	3
Benzene	C_6H_6	39
Naphthalene	$C_{10}H_8$	75
Anthracene	$C_{14}H_{10}$	105
Phenanthrene	$C_{14}H_{10}$	110
Pyridine	C_5H_5N	43
Quinoline	C_9H_7N	69
Pyrrole	C_4H_5N	31
Carbazole	$C_{12}H_9N$	91
Furan	C_4H_4O	23
Thiophene	C_4H_4S	31
Biphenyl	C_6H_5—C_6H_5	8 *
Phenylethylene	C_6H_5—CH═CH_2	7 *
Stilbene	C_6H_5—CH═CH—C_6H_5	15 *
Phenylacetylene	C_6H_5—C≡CH	10 *
Phenol	C_6H_5—OH	7 *
Aniline	C_6H_5—NH_2	6 *
Benzaldehyde	C_6H_5—(C═O)—H	4 *
Acetophenone	C_6H_5—(C═O)—CH_3	7 *
Benzophenone	C_6H_5—(C═O)—C_6H_5	10 *
Benzoic acid	C_6H_5—(C═O)—OH	4 *†
Phenyl cyanide	C_6H_5—C≡N	5 *

* Additional to the 39 of benzene.
† Additional to the 28 of acids.

SECTION 1.4   FREE ENERGY

The free energy of a substance is a thermodynamic function. It is defined by Equation 1–28.

$$F = H - TS \qquad (1\text{–}28)$$

Here H is the heat content, T is the absolute temperature, and S is a function called entropy. Free energy is an energy quantity and usually is measured in calories, sometimes in kilocalories. The change in free energy ΔF that accompanies a chemical reaction is the sum of the free energies of the products, minus the sum of the free energies of the reactants.

At constant temperature ΔF is related to ΔH by Equation 1–29.

$$\Delta F = \Delta H - T\Delta S \qquad (1\text{–}29)$$

The free-energy change is that part of the change in the heat content ΔH which theoretically can be transformed into work whereas the entropy-change term $T\Delta S$ represents that part of ΔH which is not available for doing work.

The free-energy change ΔF, which accompanies a reaction or a change in a system at constant temperature and pressure, is the thermodynamic driving force tending to make the reaction or change take place. If ΔF is negative, that is, if the free energy decreases algebraically, the reaction tends to take place as written. If ΔF is positive, that is, if it increases algebraically, the reaction tends to go in the direction opposite to that written. If ΔF is zero, the system is at equilibrium, and there is no tendency for any change to take place.

1.41   Standard Free Energies of Substances. The free energy of an element is taken as zero for its stable state under standard conditions of temperature and pressure, namely, 25°C. and 1 atmosphere. The standard free energy of formation $\Delta F°_{298}$ of a substance under the same standard conditions is the ΔF associated with the formation of 1 mole of the substance from the elements in their standard states.

Standard free-energy values of many substances are listed in Table 1–3. Listed also are the standard free-energy values of substances in other than their standard states. For a substance that is a stable solid at 25° and 1 atmosphere, there may be listed the standard free energies of the substance in the liquid state, in the vapor state at 1 atmosphere, and in the dissolved state at 1 molal concentration. If under standard conditions the substance is stable as a solid, the listed standard free energies of the liquid and the vapor will be greater algebraically than the standard free energy of the solid. This is due to the fact that these two

TABLE 1-3

FREE ENERGIES OF FORMATION OF SOME SUBSTANCES AT 25°C.

Name and Formula	$\Delta F°_{298}$, kcal.	Name and Formula	$\Delta F°_{298}$, kcal.
Acetaldehyde, $C_2H_4O(l)$	−31.73 *	Benzophenone	
Acetate ion, $CH_3CO_2^-$	−90.13 *	$C_{13}H_{10}O(s)$	31.4 §
Acetic acid, $C_2H_4O_2(g)$	−91.64 ¶	Benzoquinone,	
Acetic acid, $C_2H_4O_2(l)$	−94.91 *	$C_6H_4O_2(s)$	−21.41 §
Acetic acid, $C_2H_4O_2(aq)$	−96.62 *	Bibenzyl, $C_{14}H_{14}(s)$	60.8 §
Acetic anhydride,		Bicarbonate ion, HCO_3^-	−140.23 *
$C_4H_6O_3(l)$	−105.0 ¶	Biphenyl, $C_{12}H_{10}(l)$	60.5 ‖
Acetone, $C_3H_6O(g)$	−37.01 *	Biphenyl, $C_{12}H_{10}(s)$	60.01 ‖
Acetone, $C_3H_6O(l)$	−37.72 *	Bromate ion, BrO_3^-	5.0 ‡
Acetylene, $C_2H_2(g)$	50.03 †	Bromine, $Br_2(aq)$	0.98 ‡
Acrylic acid, $C_3H_4O_2(l)$	−69.70 *	n-Butane, $C_4H_{10}(g)$	−3.63 †
dl-Alanine, $C_3H_7O_2N(s)$	−88.75 *	Isobutane, $C_4H_{10}(g)$	−4.16 †
d-Alanine, $C_3H_7O_2N(s)$	−88.16 *	Butyl acetal (n),	
dl-Alanylglycine,		$C_{10}H_{22}O_2(l)$	−56.4 §
$C_5H_{10}O_3N_2(s)$	−116.91 *	Butyl alcohol (n),	
Ammonia, $NH_3(g)$	−3.94 ‡	$C_4H_{10}O(l)$	−40.34 *
Ammonia, $NH_3(aq)$	−6.33 ‡	Butyl alcohol (tert),	
Ammonium hydroxide,		$C_4H_{10}O(l)$	−45.0 §
$NH_4OH(aq)$	−62.99 ‡	Butyl benzene (n),	
Ammonium ion, NH_4^+	−18.96 ‡	$C_{10}H_{14}(l)$	29.67 ‖
Amyl acetate (n),		Butyl bromide (iso),	
$C_7H_{14}O_2(l)$	−81.1 ¶	$C_4H_9Br(l)$	−4.6 §
Amyl alcohol (tert),		Butyl bromide (tert),	
$C_5H_{12}O(l)$	−47.6 §	$C_4H_9Br(l)$	−5.6 §
Amyl alcohol (n),		Butene-1, $C_4H_8(g)$	16.81 †
$C_5H_{12}O(l)$	−38.87 *	Butene-2 (cis), $C_4H_8(g)$	15.57 †
Amyl butyrate (n),		Butene-2 (trans), $C_4H_8(g)$	14.80 †
$C_9H_{18}O_2(l)$	−74.9 §	Isobutylene, $C_4H_8(g)$	15.0 §
Aniline, $C_6H_7N(l)$	−36.6 *	Butyric acid (n),	
Anthracene, $C_{14}H_{10}(s)$	64.19 ‖	$C_4H_8O_2(l)$	−91.5 *
d-Arginine,		Butyrate ion (n),	
$C_6H_{14}O_2N_4(s)$	−57.03 *	$C_3H_7CO_2^-$	−87.23 *
l-Asparagine,		Carbon, diamond, $C(s)$	0.39 **
$C_4H_8O_3N_2(s)$	−126.53 *	Carbon dioxide, $CO_2(g)$	−94.24 *
l-Asparagine hydrate,		Carbon disulfide, $CS_2(g)$	17.6 §
$C_4H_{10}O_4N_2(s)$	−183.73 *	Carbon disulfide, $CS_2(l)$	17.15 §
d-Aspartic acid,		Carbon monoxide, $CO(g)$	−33.01 ‡
$C_4H_7O_4N(s)$	−174.61 *	Carbon tetrachloride,	
Benzene, $C_6H_6(g)$	30.30 ¶	$CCl_4(l)$	−15.6 ‡
Benzene, $C_6H_6(l)$	29.06 ‖	Carbonate ion, CO_3^-	−126.39 ‡
Benzoate ion, $C_6H_5CO_2^-$	−51.18 *	Carbonic acid,	
Benzoic acid, $C_7H_6O_2(l)$	−58.10 ¶	$H_2CO_3(aq)$	−148.92 *
Benzoic acid, $C_7H_6O_2(s)$	−59.05 *	Carbonyl chloride,	
Benzoic acid, $C_7H_6O_2(aq)$	−56.91 *	$COCl_2(g)$	−48.96 ‡

TABLE 1–3 (*Continued*)

FREE ENERGIES OF FORMATION OF SOME SUBSTANCES AT 25°C.

Name and Formula	$\Delta F°_{298}$, kcal.	Name and Formula	$\Delta F°_{298}$, kcal.
Carbonyl sulfide, COS(g)	−39.8 ‡§	Ether, $(C_2H_5)_2O(g)$	−29.4 ¶
Chlorine, $Cl_2(aq)$	1.63 ‡	Ether, $(C_2H_5)_2O(l)$	−29.6 ¶
Chlorobenzene,		Ethyl acetal, $C_6H_{14}O_2(l)$	−55.8 §
$C_6H_5Cl(l)$	27.8 §	Ethyl acetate, $C_4H_8O_2(g)$	−78.3 ¶
Cyanate ion, NCO^-	−23.63 ‡	Ethyl acetate, $C_4H_8O_2(l)$	−79.4 ¶
Cyanic acid, HNCO(aq)	−28.98 ‡	Ethyl alcohol, $C_2H_6O(g)$	−40.21 ‖
Cyanide ion, CN^-	39.14 ‡	Ethyl alcohol, $C_2H_6O(l)$	−41.73 ‖
Cyanogen, $C_2N_2(g)$	91.00 §	Ethyl alcohol,	
Cyclohexane, $C_6H_{12}(g)$	7.13 ¶	$C_2H_6O(aq., 1\ M)$	−43.35 ‖
Cyclohexane, $C_6H_{12}(l)$	5.91 ‖	Ethyl benzene, $C_8H_{10}(l)$	28.09 ‖
Cyclohexanol, $C_6H_{12}O(l)$	−34.3 §	Ethyl bromide,	
Cyclohexene, $C_6H_{10}(l)$	18.2 §	$C_2H_5Br(l)$	−6.18 §
p-Cymene, $C_{10}H_{14}(l)$	24.6 §	Ethyl *n*-butyrate,	
n-Decane, $C_{10}H_{22}(l)$	−3.49 ‖	$C_6H_{12}O_2(l)$	−77.6 ¶
l-Cysteine, $C_3H_7O_2NS(s)$	−82.48 ††	Ethylcyclohexane,	
l-Cystine,		$C_8H_{16}(l)$	8.00 ‖
$C_6H_{12}O_4N_2S_2(s)$	−166.63 ††	Ethylene, $C_2H_4(g)$	16.33 ‖
Dibenzoylethane,		Ethylene glycol,	
$C_{16}H_{14}O_2(s)$	−2.5 §	$C_2H_6O_2(l)$	−80.2 §
Dibenzoylethylene,		Ethylene iodide,	
$C_{16}H_{12}O_2(s)$	21.5 §	$C_2H_4I_2(s)$	13.8 ¶
Di-isobutylene, $C_8H_{16}(l)$	21.8 §	Ethyl mercaptan,	
Dimethyl acetal,		$C_2H_6S(l)$	0.8 §
$C_4H_{10}O_2(l)$	−55.1 ¶	Ethyl sulfide, $C_4H_{10}S(l)$	5.3 §
1,2-Dimethylcyclopen-		Ferric ion, Fe^{+++}	−2.53 ‡
tane, $C_7H_{14}(l)$	1.0 §	Ferrous ion, Fe^{++}	−20.31 ‡
Dimethyl ether,		Formaldehyde, $CH_2O(g)$	−27.30 *
$C_2H_6O(g)$	−26.9 ¶	Formaldehyde,	
o-Dinitrobenzene,		$CH_2O(aq)$	−32.17 *
$C_6H_4O_4N_2(s)$	49.4 ‖	Formic acid, $CH_2O_2(g)$	−82.46 ¶
m-Dinitrobenzene,		Formic acid, $CH_2O_2(l)$	−85.09 *
$C_6H_4O_4N_2(s)$	42.9 ‖	Formic acid, $CH_2O_2(aq)$	−88.05 *
Diphenylmethane,		Fumarate ion, $C_4H_2O_4^=$	−144.39 *
$C_{13}H_{12}(s)$	63.6 ‖	Fumaric acid, $C_4H_4O_4(s)$	−156.40 *
Diphenylcarbinol,		Fumaric acid,	
$C_{13}H_{12}O(s)$	30.7 ‖	$C_4H_4O_4(aq)$	−154.66 *
n-Dodecane, $C_{12}H_{26}(l)$	3.9 ‖	*d*-Glucose-α, $C_6H_{12}O_6(s)$	−217.48 *
Dulcitol, $C_6H_{14}O_6(s)$	−223.1 ‖	*d*-Glucose-β, $C_6H_{12}O_6(s)$	−217.06 *
Durene, $C_{10}H_{14}(l)$	19.7 ‖	*d*-Glutamic acid,	
Durene, $C_{10}H_{14}(s)$	19.0 ‖	$C_5H_9O_4N(s)$	−173.76 *
Durene (*iso*), $C_{10}H_{14}(l)$	15.9 ‖	Glycerol, $C_3H_8O_3(l)$	−113.05 *
dl-Erythritol,		Glycine, $C_2H_5O_2N(s)$	−88.5 *
$C_4H_{10}O_4(s)$	−149.4 §	Glycylglycine,	
Ethane, $C_2H_6(g)$	−7.45 *	$C_4H_8O_3N_2(s)$	−117.75 *

TABLE 1–3 (*Continued*)

FREE ENERGIES OF FORMATION OF SOME SUBSTANCES AT 25°C.

Name and Formula	$\Delta F°_{298}$, kcal.	Name and Formula	$\Delta F°_{298}$, kcal.
n-Heptane, $C_7H_{16}(l)$	0.00 ‖	Hydrogen iodide, HI(g)	0.315 **
3-Ethylpentane, $C_7H_{16}(l)$	−1.80 §	Hydrogen iodide, HI(aq)	−12.30 ‡
3,3-Dimethylpentane, $C_7H_{16}(l)$	−2.40 §	Hydrogen peroxide, $H_2O_2(l)$	−28.23 ‡
2,4-Dimethylpentane, $C_7H_{16}(l)$	−1.30 §	Hydrogen peroxide, $H_2O_2(aq)$	−31.47 ‡
2,2-Dimethylpentane, $C_7H_{16}(l)$	−1.80 §	Hydrogen sulfide, $H_2S(g)$	−7.87 ‡
2,3-Dimethylpentane, $C_7H_{16}(l)$	−2.10 §	Hydrogen sulfide, $H_2S(aq)$	−6.52 ‡
2-Methylhexane, $C_7H_{16}(l)$	−3.00 §	Hydroquinone, $C_6H_6O_2(s)$	−52.7 §
3-Methylhexane, $C_7H_{16}(l)$	−2.60 §	Hydrosulfide ion, HS⁻	2.95 ‡
2,2,3-Trimethyl-butane, $C_7H_{16}(l)$	−0.80 §	Hypobromous acid, HBrO(aq)	−19.9 ‡
Hexamethylbenzene, $C_{12}H_{18}(l)$	26.90 §	Hypochlorite ion, ClO⁻	−9.2 ‡
Hexamethylbenzene, $C_{12}H_{18}(s)$	25.20 §	Hypochlorous acid, HClO(aq)	−19.1 ‡
Hexamethylethane, $C_8H_{18}(l)$	−1.50 §	Hypoiodous acid, HIO(aq)	−23.3 ‡
Hexamethylethane, $C_8H_{18}(s)$	1.20 §	Iodate ion, IO₃⁻	−32.3 ‡
n-Hexane, $C_6H_{14}(l)$	−1.08 ‖	Iodine, $I_2(aq)$	3.9 ‡
n-Hexyl alcohol, $C_6H_{14}O(l)$	−37.34 *	dl-Lactic acid, $C_3H_6O_3(l)$	−124.4 §
Hippuric acid, $C_9H_9O_3N(s)$	−88.56 *	dl-Leucine, $C_6H_{13}O_2N(s)$	−83.27 *
Hydrogen bromide, HBr(g)	−12.54 **	l-Leucine, $C_6H_{13}O_2N(s)$	−82.50 *
Hydrogen bromide, HBr(aq)	−24.58 ‡	dl-Leucylglycine, $C_8H_{16}O_3N_2(s)$	−112.13 *
Hydrogen chloride, HCl(g)	−22.69 **	l-Malate ion, $C_4H_4O_5^-$	−201.8 *
Hydrogen chloride, HCl(aq)	−31.33 ‡	Maleic acid, $C_4H_4O_4(s)$	−150.49 *
Hydrogen cyanide, HCN(g)	27.73 ‡	l-Malic acid, $C_4H_6O_5(s)$	−211.45 §
Hydrogen cyanide, HCN(l)	28.00 ‡	l-Malic acid, $C_4H_6O_5(aq)$	−213.5 §
Hydrogen cyanide, HCN(aq)	26.34 ‡	Mannitol, $C_6H_{14}O_6(s)$	−222.2 §
		Methane, $CH_4(g)$	−12.2 *
		Methyl alcohol, $CH_4O(g)$	−38.65 ¶
		Methyl alcohol, $CH_4O(l)$	−39.72 *
		Methylcyclohexane, $C_7H_{14}(l)$	4.28 ‖
		Methylcyclopentane, $C_6H_{12}(l)$	6.88 ‖
		Methyl formate, $C_2H_4O_2(g)$	−70.5 ¶
		Methyl formate, $C_2H_4O_2(l)$	−70.8 ¶

TABLE 1–3 (*Continued*)

FREE ENERGIES OF FORMATION OF SOME SUBSTANCES AT 25°C.

Name and Formula	$\Delta F°_{298}$, kcal.	Name and Formula	$\Delta F°_{298}$, kcal.
Methyl nitrite,		2-Methylbutane,	
$CH_3O_2N(g)$	0.0 ¶	$C_5H_{12}(l)$	−3.3 §
Naphthalene, $C_{10}H_8(l)$	48.1 ¶	Phenanthrene, $C_{14}H_{10}(s)$	54.09 ‖
Naphthalene, $C_{10}H_8(s)$	47.43 ‖	Phenol, $C_6H_6O(s)$	−11.0 §
Nitrate ion, NO_3^-	−26.3 ‡	Picric acid, $C_6H_3O_7N_3(s)$	10.0 §
Nitric acid, $HNO_3(g)$	−18.21 **	Prehnitene, $C_{10}H_{14}(l)$	20.2 §
Nitric acid, $HNO_3(aq)$	−26.50 **	Propane, $C_3H_8(g)$	−5.55 †
Nitrite ion, NO_2^-	−8.5 ‡	Propionic acid,	
o-Nitroaniline,		$C_3H_6O_2(aq)$	−91.26 *
$C_6H_6O_2N_2(s)$	41.4 §	Propyl acetal (*n*),	
m-Nitroaniline,		$C_8H_{18}O_2(l)$	−57.2 §
$C_6H_6O_2N_2(s)$	40.4 §	Propyl acetal (*iso*),	
p-Nitroaniline,		$C_8H_{18}O_2(l)$	−61.9 §
$C_6H_6O_2N_2(s)$	36.4 §	Propyl alcohol (*n*),	
Nitrobenzene,		$C_3H_8O(aq)$	−41.32 *
$C_6H_5O_2N(l)$	36.4 §	Propyl alcohol (*iso*),	
o-Nitrobenzoic acid,		$C_3H_8O(l)$	−43.75 *
$C_7H_5O_4N(s)$	−48.4 §	Propylene, $C_3H_6(g)$	14.73 †
m-Nitrobenzoic acid,		Pseudocumene, $C_9H_{12}(l)$	21.0 §
$C_7H_5O_4N(s)$	−54.2 §	Pyrene, $C_{16}H_{10}(s)$	26.9 ‖
p-Nitrobenzoic acid,		Pyrocatechol, $C_6H_6O_2(s)$	51.4 §
$C_7H_5O_4N(s)$	−55.5 §	Quinhydrone,	
Nitrogen dioxide,		$C_{12}H_{10}O_4(s)$	−77.19 §
$NO_2(g)$	12.3 ‡	Resorcinol, $C_6H_6O_2(s)$	−53.2 §
Nitrogen tetroxide,		Silver ion, Ag^+	18.45 ‡
$N_2O_4(g)$	23.44 ‡	Stilbene, $C_{13}H_{14}(s)$	75.8 §
Nitrosyl chloride,		Succinate ion, $C_4H_4O_4^-$	−165.09 §
$NOCl(g)$	16.01 ‡	Succinic acid, $C_4H_6O_4(s)$	−178.53 *
Nitrous acid, $HNO_2(aq)$	−13.07 ‡	Succinic acid,	
n-Nonane, $C_9H_{20}(l)$	2.28 †	$C_4H_6O_4(aq)$	−178.24 *
n-Octane, $C_8H_{18}(g)$	3.4 †	Sucrose, $C_{12}H_{22}O_{11}(s)$	−370.14 *
n-Octane, $C_8H_{18}(l)$	1.11 ‖	Sulfur dioxide, $SO_2(g)$	−71.7 ‡
2,2,4-Trimethylpentane,		Sulfuric acid, $H_2SO_4(aq)$	−176.5 ‡
$C_8H_{18}(l)$	−0.8 §	Sulfurous acid,	
n-Octyl alcohol,		$H_2SO_3(aq)$	−128.5 ‡
$C_8H_{18}O(l)$	−35.1 §	Tetramethylmethane,	
Oleic acid, $C_{18}H_{34}O_2(l)$	−53.16 *	$C_5H_{12}(l)$	−3.31 †
Oxalic acid, $H_2C_2O_4(s)$	−165.52 §	Tetraphenylmethane,	
Ozone, $O_3(g)$	39.4 ‡	$C_{25}H_{20}(s)$	−137.7 §
Palmitic acid,		Thiophene, $C_4H_4S(l)$	26.3 §
$C_{16}H_{32}O_2(s)$	−76.76 *	Toluene, $C_7H_8(l)$	27.97 ‖
Pentacosane, $C_{25}H_{52}(l)$	15.0 §	Trimethylethylene,	
Pentacosane, $C_{25}H_{52}(s)$	13.4 §	$C_5H_{10}(l)$	13.7 §
Pentamethylbenzene,		Triphenylamine,	
$C_{11}H_{16}(s)$	21.9 §	$C_{18}H_{15}N(s)$	120.5 §
n-Pentane, $C_5H_{12}(l)$	−8.6 §		

TABLE 1-3 (*Continued*)

FREE ENERGIES OF FORMATION OF SOME SUBSTANCES AT 25°C.

Name and Formula	$\Delta F°_{298}$, kcal.	Name and Formula	$\Delta F°_{298}$, kcal.
1,3,5-Triphenylbenzene,		Triphenylmethane,	
$C_{24}H_{18}(s)$	120.24 ‖	$C_{19}H_{16}(s)$	101.4 §
Triphenylbromomethane,		Undecane, $C_{11}H_{24}(l)$	4.31 ‖
$C_{19}H_{15}Br(s)$	107.7 §	Urea, $CH_4N_2O(s)$	−47.12 §
Triphenylcarbinol,		Urea, $CH_4N_2O(aq)$	−48.72 §
$C_{19}H_{16}O(s)$	69.7 §	Water, $H_2O(g)$	−54.63 ‡
Triphenylchloromethane,		Water, $H_2O(l)$	−56.69 ‡
$C_{19}H_{15}Cl(s)$	100.6 §	o-Xylene, $C_8H_{10}(l)$	27.3 §
Triphenylethylene,		m-Xylene, $C_8H_{10}(l)$	27.0 §
$C_{20}H_{16}(s)$	123.0 §	p-Xylene, $C_8H_{10}(l)$	23.2 §

Sources of data:

* H. Borsook, private communication.

† K. Pitzer, *Chem. Rev.*, **27**, 39 (1940).

‡ W. Latimer, *The Oxidation States of the Elements and their Potentials in Aqueous Solutions*, Prentice-Hall, New York, 1938.

§ G. Parks and H. Huffman, *The Free Energies of Some Organic Compounds*, Chemical Catalog Co., New York, 1932.

‖ G. Parks, private communication and *Chem. Rev.*, **27**, 75 (1940).

¶ Recalculated from ref. § using data of *, †, ‡, ‖.

** G. N. Lewis and M. Randall, *Thermodynamics*, McGraw-Hill Book Co., New York, 1923.

†† H. Borsook and H. Huffman, *The Chemistry of the Amino Acids and Proteins*, edited by C. L. A. Schmidt, Charles C. Thomas, Springfield, Ill., 1938.

states are unstable with respect to the solid state. The standard free energy of a substance in a 1 molal solution will, relative to the pure substance, have an algebraically lower free-energy value if the solution is not saturated, a higher value if the solution is supersaturated, and the same value if the solution is just saturated. The actual free energy of formation of 1 mole of a substance as a saturated vapor, or in a saturated solution, is the same as the standard free energy of the substance in its stable state, since there is no tendency for any change to take place in either direction.

Ions also are listed in the table of free energies. The values are for 1 M solutions and are based on the value of zero for hydrogen ion.

The standard free-energy values of substances in solution and in the vapor state, as listed in Table 1-3, are the values extrapolated from very low concentrations and pressures, where the substances behave in an ideal manner.

1.42 Free-Energy Change as Related to Equilibrium. The equilibrium constant of a reaction is determined, at constant pressure
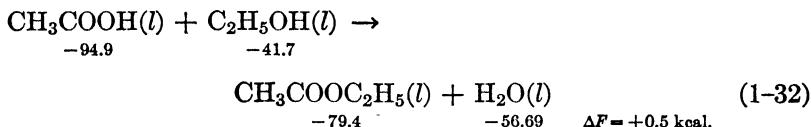
and temperature, by the change in the standard free energy taking place during the reaction, through the relationship of Equation 1–30.

$$-\Delta F^{\circ}{}_{298} = RT \ln K \qquad (1\text{--}30)$$

Here $\Delta F^{\circ}{}_{298}$ is expressed in calories per mole, R is the gas constant, 1.99 cal. per mole per degree, and $\ln K$ is the natural logarithm of the equilibrium constant. A more convenient form is Equation 1–31, in which $\Delta F^{\circ}{}_{298}$ is expressed as kilocalories:
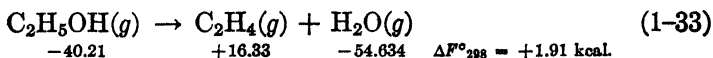
$$\log_{10} K = -\Delta F^{\circ}{}_{298}/1.363 \qquad (1\text{--}31)$$

The method by which free energies can be used to calculate equilibrium constants is illustrated by the liquid-phase reaction at 25° between acetic acid and ethyl alcohol to form ethyl acetate and water, according to Equation 1–32.

$$\underset{-94.9}{CH_3COOH(l)} + \underset{-41.7}{C_2H_5OH(l)} \rightarrow$$

$$\underset{-79.4}{CH_3COOC_2H_5(l)} + \underset{-56.69}{H_2O(l)} \qquad \underset{\Delta F\,=\,+0.5\ kcal.}{} \qquad (1\text{--}32)$$

Here the free energies of formation in the liquid state are written below the respective formulas. The sum of these values for the reactants is -136.6 kcal., and for the products, -136.1 kcal. The difference, namely, 0.5 kcal., represents an increase in free energy while the reaction is taking place, that is, $\Delta F^{\circ}{}_{298}$ is $+0.5$ kcal. On substituting in Equation 1–31, a value of -0.4 is obtained for $\log_{10} K$, and of 0.16 for K, the equilibrium constant for the liquid-phase reaction. It was mentioned on page 13 that the equilibrium constant for the liquid-phase reaction, as expressed in Equation 1–14, is 4. In this case there is reasonably good agreement between the experimental and calculated values, considering that the value of $+0.5$ is a small difference between large values. When ΔF is calculated from the equilibrium constant, 4, the value should be -0.8 kcal.

Another example of the use of free energies to calculate equilibrium constants is the hypothetical gas-phase dehydration of ethyl alcohol to ethylene and water at 25° and 1 atmosphere, according to Equation 1–33.

$$\underset{-40.21}{C_2H_5OH(g)} \rightarrow \underset{+16.33}{C_2H_4(g)} + \underset{-54.634}{H_2O(g)} \qquad \underset{\Delta F^{\circ}{}_{298}\,=\,+1.91\ kcal.}{} \qquad (1\text{--}33)$$

Here the algebraic sum of the products exceeds that of the reactants by 1.91 kcal. Therefore there is an increase in the free energy, that is, $\Delta F^{\circ}{}_{298}$ is $+1.91$ kcal. The equilibrium constant K has a value of 0.04 by calculation with the use of Equation 1–31. In this case the constant

is such that a measurable equilibrium is to be expected. Moreover, if reaction could take place at this temperature (actually no reaction takes place in either direction because the rate is essentially zero), the equilibrium would lie well on the side of ethyl alcohol.

Only when the free-energy change is small does a practical equilibrium for a reaction exist. Thus for a bimolecular reaction of the ethyl acetate type (Equation 1–32) the equilibrium lies 91% to the right if $\Delta F°_{298}$ is -2.7 kcal. ($K = 100$); it lies only 9% to the right if $\Delta F°_{298}$ is $+2.7$ kcal. ($K = \frac{1}{100}$); it lies closer to 50% as the $\Delta F°_{298}$ values become numerically smaller. Thus practical equilibria occur only when the magnitude of the free-energy change lies approximately between $+3$ and -3 kcal. However, if $\Delta F°_{298}$ has a value greater than about $+3$ kcal., the reaction is still practical if at least one of the reaction products can be removed.

1.43 Approximation of ΔF from ΔH. Often it is possible to obtain a useful approximation of ΔF from ΔH. The two extreme conditions under which this can be done, without the actual value of $T\Delta S$ the entropy-change term being known, occur when (1) ΔH is large and (2) $T\Delta S$ is small.

When the numerical value of ΔH is greater than about 20 kcal., ΔF almost invariably will have the same sign as ΔH and also a numerical value greater than about 5 kcal. This is due to the fact that the numerical value of $T\Delta S$, with a relatively few exceptions, does not exceed 15 kcal. and in general seldom exceeds 10 kcal. The reaction, therefore, is not of the equilibrium type. The direction the reaction takes is indicated by the sign of ΔH.

When $T\Delta S$ is small (± 1 or 2 kcal.), ΔF will have approximately the same value as ΔH. If ΔH is sufficiently large ($> \pm 2$ kcal.), ΔF has the same sign as ΔH. The magnitude of $T\Delta S$ is small when reactants and products are alike in regard to (1) number of molecules, (2) complexity of molecules, and (3) physical state. An increase in the entropy of the system ($T\Delta S$ is positive) accompanies (1) an increase in the number of molecules, (2) change from a more rigid to a less rigid structure, (3) change from the solid to the liquid or gaseous state, and (4) change from the liquid to the gaseous state.

Even when ΔH is less than about 15 kcal. and $T\Delta S$ is not small, the reaction will not be of the equilibrium type if $T\Delta S$ has the opposite sign to ΔH. If $T\Delta S$ has the same sign as ΔH, a reasonably accurate value of $T\Delta S$ is needed before ΔF can be approximated from ΔH.

A typical reaction in which the $T\Delta S$ term has a small value is the gas-phase reaction of hydrogen with chlorine:

$$H_2 + Cl_2 \rightarrow 2HCl \qquad (1\text{--}34)$$

Here ΔH_{298} is -22.026 kcal., and ΔF°_{298} is -22.692 kcal. The value of $T\Delta S$ therefore is only $+0.666$ kcal.

The $T\Delta S$ term likewise has a small value in the liquid-phase reaction of acetic acid with ethyl alcohol. Here ΔH_{298} is $+0.8$ kcal. from heats of combustion (Equation 1–24), and ΔF°_{298} is $+0.5$ kcal. (Equation 1–32). Thus $T\Delta S$ is $+0.3$ kcal. However, this result should not be taken too seriously since a small percentage error in the ΔH or ΔF values of any of the individual compounds can affect this result markedly.

In the hypothetical gas-phase dehydration of ethyl alcohol to ethylene at 25°, the $T\Delta S$ term is $+8.4$; ΔH is $+10.3$ kcal. (Equation 1–22, correcting for heats of vaporization, as in Subsection 1.35), and ΔF°_{298} is $+1.91$ kcal. (Equation 1–33). The increase in entropy here is due to the fact that the number of products exceeds the number of reactants. In this instance $T\Delta S$ is large, relative to ΔH. In other cases where $T\Delta S$ is large, relative to ΔH, the sign of ΔF may actually be opposite to that of ΔH. This relationship is not a very common one. It may occur when ΔH is less than 15 kcal.
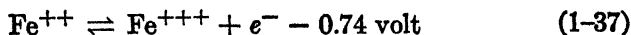
1.44 Molal-Reduction Potentials. In oxidation–reduction systems it often is more convenient to use molal-reduction potentials, rather than standard free-energy values for calculating equilibrium constants, since the molal-reduction potential gives directly the power of a certain oxidation–reduction couple, whether for an oxidation–reduction half-cell, or for the whole cell of a complete reaction. The electric potential is related to the standard free-energy change by Equation 1–35.
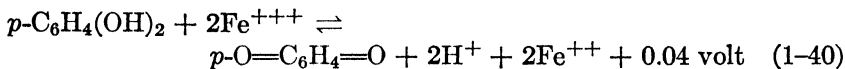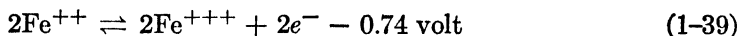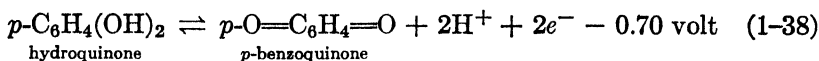
$$\Delta F^{\circ}_{298} = -NE^{\circ}_{298}\,\mathbf{F} \qquad (1\text{--}35)$$

Here N is the number of moles of electricity passed, $\mathbf{F}$ is the number of coulombs per equivalent, and E°_{298} is the electromotive force, when the concentrations of all dissolved substances are 1 M, and the pressures of all gases are 1 atmosphere. If E°_{298} is in volts, and ΔF°_{298} is in kilocalories, the foregoing expression reduces to Equation 1–36, since 1 electron volt is 23.06 kcal. per mole.

$$\Delta F^{\circ}_{298} = -23.06NE^{\circ}_{298} \qquad (1\text{--}36)$$

When two molal-reduction equations are combined to form the equation of a reaction, for instance, the equation for the oxidation of hydroquinone by ferric ion, the resulting potential is a measure of the tendency of the reaction to proceed as written when the concentrations of all soluble components are 1 M.

$$\mathrm{Fe^{++}} \rightleftharpoons \mathrm{Fe^{+++}} + e^{-} - 0.74 \text{ volt} \qquad (1\text{--}37)$$

$$p\text{-}C_6H_4(OH)_2 \rightleftharpoons p\text{-}O\!=\!C_6H_4\!=\!O + 2H^+ + 2e^- - 0.70 \text{ volt} \quad (1\text{-}38)$$
<p style="text-align:center">hydroquinone   p-benzoquinone</p>

$$2Fe^{++} \rightleftharpoons 2Fe^{+++} + 2e^- - 0.74 \text{ volt} \quad (1\text{-}39)$$

$$p\text{-}C_6H_4(OH)_2 + 2Fe^{+++} \rightleftharpoons$$
$$p\text{-}O\!=\!C_6H_4\!=\!O + 2H^+ + 2Fe^{++} + 0.04 \text{ volt} \quad (1\text{-}40)$$

The ferrous–ferric half cell is represented by Equations 1–37 and 1–39 (the molal-reduction potential, -0.74 volt, is not altered by the multiplication) and the hydroquinone–quinone half-cell is represented by Equation 1–38. By combining Equations 1–38 and 1–39 so as to cancel the e^-'s, Equation 1-40 is obtained for the balanced oxidation–reduction reaction involving ferrous ion, ferric ion, hydroquinone, and quinone, and for the value of $E_0{}^{25}$, namely, $+0.04$ volt. A positive potential indicates that the reaction tends to proceed as written. The potential tells nothing about the rate.

The equilibrium constant K for a complete reaction between an oxidizing agent and a reducing agent is given by Equation 1–41, which is obtained by combining Equations 1–31 and 1–36.

$$\log K = \Delta E^\circ{}_{298} N_{e^-}/0.06 \quad (1\text{-}41)$$

Here $\Delta E^\circ{}_{298}$ is the combined electrode potential of the half reactions, and N_{e^-} is the number of e^-'s that were taken in the calculation.

The equilibrium constant for the reaction shown in Equation 1–40 is obtained by making the proper substitutions in Equation 1–41, as shown in Equations 1–42 and 1–43.

$$\log K = \frac{0.04 \times 2}{0.06} = 1.33 \quad (1\text{-}42)$$

$$K = 21 = \frac{(C_6H_4O_2)(H^+)^2(Fe^{++})^2}{(C_6H_6O_2)(Fe^{+++})^2} \quad (1\text{-}43)$$

Molal-reduction potentials of many oxidation–reduction half-cells are shown in Table 1–4.

1.45 Nondependence of Rate on ΔH and ΔF. *In no way can the rate of reaction be predicted from the change in the heat content or the change in the free energy of the system.* No matter what the potential heat change or free-energy change may be, nothing can be said regarding the rate with which the reaction will proceed. For example, no reaction appears to take place when ethyl alcohol stands in contact with oxygen of the air at room temperature, although 327 kcal. of heat are liberated and the free energy decreases by 318 kcal. when 1 mole of alcohol burns

to carbon dioxide and water. Only when the alcohol is raised to the ignition temperature does the rate become high enough for the reaction to proceed spontaneously.

TABLE 1–4

MOLAL-REDUCTION POTENTIALS AT 25°C.

Reaction	$E°_{298}$, volts	Reaction	$E°_{298}$, volts
$Li = Li^+ + e^-$	$+2.957$	$Fe^{++} = Fe^{+++} + e^-$	-0.74
$Na = Na^+ + e^-$	$+2.712$	$2Hg = Hg_2^{++} + 2e^-$	-0.798
$Mg = Mg^{++} + 2e^-$	$+2.40$	$Ag = Ag^+ + e^-$	-0.799
$Al = Al^{+++} + 3e^-$	$+1.7$	$Hg = Hg^{++} + 2e^-$	-0.86
$S_2O_4^= + 4OH^- = 2SO_3^= +$		$C_6H_5NH_3^+ + 2H_2O =$	
$\quad 2H_2O + 2e^-$	$+1.4$	$\quad C_6H_5NO_2 + 7H^+ + 6e^-$	-0.87
$\frac{1}{2}H_2 + OH^- = H_2O + e^-$	$+0.828$	$Hg_2^{++} = 2Hg^{++} + 2e^-$	-0.92
$Zn = Zn^{++} + 2e^-$	$+0.758$	$Cl^- + 2OH^- = ClO^- +$	
$Zn + 3OH^- = HZnO_2^- +$		$\quad H_2O + 2e^-$	-0.94
$\quad H_2O + 2e^-$	$+0.72$	$NO + 2H_2O = NO_3^- +$	
$Fe(OH)_2 + OH^- =$		$\quad 4H^+ + 3e^-$	-0.94
$\quad Fe(OH)_3 + e^-$	$+0.65$	$HNO_2 + H_2O = NO_3^- +$	
$Pb + 2OH^- = PbO +$		$\quad 3H^+ + 2e^-$	-0.95
$\quad H_2O + 2e^-$	$+0.58$	$2Br^- = Br_2 + 2e^-$	-1.065
$S^= = S + 2e^-$	$+0.51$	$I^- + 3H_2O = IO_3^- +$	
$H_2Se = Se + 2H^+ + 2e^-$	$+0.5$	$\quad 6H^+ + 6e^-$	-1.09
$Fe = Fe^{++} + 2e^-$	$+0.44$	$2H_2O = O_2 + 4H^+ + 4e^-$	-1.23
$H_2 = 2H^+(10^{-7}\,M) + 2e^-$	$+0.414$	$Cr^{+++} + 4H_2O =$	
$HS_2O_4^- + 2H_2O =$		$\quad HCrO_4^- + 7H^+ + 3e^-$	-1.3
$\quad 2H_2SO_3 + H^+ + 2e^-$	$+0.23$	$Mn^{++} + 2H_2O = MnO_2 +$	
$Sn = Sn^{++} + 2e^-$	$+0.13$	$\quad 4H^+ + 2e^-$	-1.33
$H_2 = 2H^+ + 2e^-$	0.000	$2Cl^- = Cl_2 + 2e^-$	-1.359
$Ti^{+++} + H_2O = TiO^{++} +$		$I^- + 4H_2O = IO_4^- +$	
$\quad 2H^+ + e^-$	-0.04	$\quad 8H^+ + 8e^-$	-1.4
$Hg + 2OH^- = HgO +$		$Br^- + 3H_2O = BrO_3^- +$	
$\quad H_2O + 2e^-$	-0.099	$\quad 6H^+ + 6e^-$	-1.42
$Sn^{++} = Sn^{++++} + 2e^-$	-0.13	$Pb^{++} + 2H_2O = PbO_2 +$	
$H_2SO_3 + H_2O = H_2SO_4 +$		$\quad 4H^+ + 2e^-$	-1.44
$\quad 2H^+ + 2e^-$	-0.14	$Cl^- + 3H_2O = ClO_3^- +$	
$H_2S = S + 2H^+ + 2e^-$	-0.17	$\quad 6H^+ + 6e^-$	-1.45
$Ag + 2NH_3(aq) =$		$Cl^- + H_2O = HClO +$	
$\quad Ag(NH_3)_2^+ + e^-$	-0.373	$\quad H^+ + 2e^-$	-1.50
$4OH^- = O_2 + 2H_2O + 4e$	-0.40	$2SO_4^- + 2H^+ = H_2S_2O_8 +$	
$Fe(CN)_6^{===} = Fe(CN)_6^{≡} +$		$\quad 2e^-$	$ca. -1.5$
$\quad e^-$	-0.49	$Mn^{++} + 4H_2O =$	
$H_3AsO_3 + H_2O =$		$\quad MnO_4^- + 8H^+ + 5e^-$	-1.52
$\quad H_3AsO_4 + 2H^+ + 2e^-$	-0.49	$MnO_2 + 2H_2O =$	
$2I^- = I_2 + 2e^-$	-0.535	$\quad MnO_4^- + 4H^+ + 2e^-$	-1.63
$3I^- = I_3^- + 2e^-$	-0.54	$2H_2O = H_2O_2 + 2H^+ +$	
$H_2O_2 = O_2 + 2H^+ + 2e^-$	-0.68	$\quad 2e^-$	-1.78
$C_6H_4(OH)_2 = C_6H_4(O)_2$		$O_2 + H_2O = O_3 + 2H^+ +$	
$\quad (quinone) + 2H^+ + 2e^-$	-0.70	$\quad 2e^-$	-1.9
		$2F^- = F_2 + 2e^-$	-2.8

SECTION 1.5 FACTORS THAT DETERMINE YIELDS

In the preparation of organic compounds it is desirable to obtain the highest yield possible with the least amount of effort and expense. Aside from losses connected with mechanical manipulations, this is accomplished in two ways: (1) by driving the reaction to completion, and (2) by eliminating side reactions. The reaction may be driven to completion from a practical point of view by increasing the rate of reaction or by shifting the point of equilibrium, if one exists. The rate may be increased by adding a catalyst, by raising the temperature, or by increasing the concentration of one or more of the reactants. For heterogeneous reactions the extent of subdivision and the vigor of agitation are also important rate factors. The control of the temperature is important, so that the reaction will proceed rapidly and smoothly without getting out of hand. Hence a knowledge of the heat of reaction is helpful, and the calculation of an approximate value may be made from known bond-energy and resonance-energy values. When an equilibrium exists, it may be shifted toward completion by using an excess of one reagent or by changing the temperature if there is an appreciable temperature coefficient of the equilibrium constant. The reaction actually may be driven to completion by the removal of one or more of the products as they are formed.

Side reactions may be minimized by the control of concentrations or temperature, or by the use of catalysts to increase the prominence of one reaction. If the product undergoes subsequent reactions it should be isolated as it is formed.

In actual laboratory practice all the foregoing considerations should be taken into account in order to obtain the most favorable balance between yield, expense, and the time involved in a laboratory preparation.

Chapter 2

SOLUBILITY

It was shown in Chapter 1 that solvents are useful for decreasing the rate of very fast reactions by dilution, for regulating temperature, and for converting heterogeneous systems to homogeneous systems. The likelihood of making a satisfactory selection of solvent is enhanced by a good knowledge of solubility relationships and an understanding of the principles underlying these.

In the separation and purification of organic compounds in the course of their preparation, constant use is made of solubility relationships. Some of the operations in which solubility plays an important part are: the scrubbing of gases, the distillation of liquid mixtures, the extraction of a liquid or a solid from a reaction mixture by means of a suitable solvent, the precipitation of a reaction product by the addition of a suitable solvent, the crystallization of a solid from a suitable solvent, and the washing of a solid. Therefore a thorough understanding of solubility relationships is desirable.

SECTION 2.1 TYPES OF SOLVENTS

2.11 Inert Solvents. When a substance can be recovered unchanged from its solution in a given solvent by purely physical means, as for example by evaporation, the solvent is called an inert solvent.

It is possible for a chemical change to accompany the dissolving of a substance in an inert solvent, as for example the formation of hydrates in solution, which may be the basis of the actual dissolving action, but this is immaterial, provided only that the substance is recoverable unchanged.

2.12 Reaction Solvents. When the substance recovered from a solution after the solvent has been removed by physical means is different from the original substance, the solvent is called a reaction solvent. A reaction solvent usually is not a pure solvent but a solution of some reactive compound in an inert solvent, usually water. The reactive compound usually is an acid or a base.

Compounds that ordinarily do not dissolve in water often can be put into solution by reacting to form a soluble substance, as for example a

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soluble salt. Thus many acids, inorganic as well as organic, dissolve in dilute aqueous solutions of sodium carbonate, sodium hydroxide, and so on, even though the acids themselves are not soluble in water. Conversely, many insoluble bases dissolve in dilute aqueous solutions of acids, such as hydrochloric and hydrobromic acid. The original insoluble acid can be recovered from the solution by the addition of a suitable soluble strong acid, and the insoluble base can be recovered by the addition of a suitable soluble strong base. These two operations of solution and precipitation are of great value in the separation of reactive insoluble substances from inert insoluble substances.

In some cases the solvent itself reacts with the substance, especially if it is an acid halide, an acid anhydride, or an ester. Thus, when phosphorus trichloride is added to water, reaction takes place with the formation of phosphorous acid and hydrochloric acid.

<center>SECTION 2.2 STRUCTURAL FACTORS IN SOLUBILITY</center>

2.21 Effect of Similarity of Structure. High mutual solubilities are characteristic of liquid compounds whose molecules are similar in structure and size. Because each liquid of such a pair is very soluble in the other, the two liquids are miscible in all proportions (see Subsection 2.33). Closely related compounds, as for example adjacent members of homologous series such as n-hexane C_6H_{14} and n-heptane C_7H_{16} or methyl alcohol CH_3OH and ethyl alcohol C_2H_5OH, form perfect solutions. They obey Raoults' law; that is, their vapor pressures are proportional to their mole fractions (see Subsection 9.11).

On the other hand liquids are insoluble in each other when they differ markedly in structure. Thus water H_2O and hexane C_6H_{14} do not mix and do not dissolve in each other, except to a minute extent; also ethylene glycol $C_2H_4O_2$ and hexane C_6H_{14} do not dissolve in each other. As molecules become more alike, mutual solubilities increase. Thus, water is more soluble in hexyl alcohol $C_6H_{13}OH$ than in hexane, and the solubility of water increases as the number of carbon atoms in the organic molecule decreases.

Propyl alcohol C_3H_7OH and the lower alcohols are miscible with water in all proportions. On the other hand, the mutual solubility of hexane with an oxygen containing organic solvent decreases as that of water increases. Although hexane is miscible with propyl alcohol, it is not with methyl alcohol CH_3OH.

Some interesting deductions can be drawn from the data of Table 2–1, the solubility of the solid aromatic hydrocarbon, naphthalene $C_{10}H_8$, in different solvents. Molal solubilities, last column, are more significant

TABLE 2-1

SOLUBILITY OF NAPHTHALENE $C_{10}H_8$ IN DIFFERENT SOLVENTS AT 20°

Solvent	Structure	Naphthalene per 100 g. of Solvent, g.	Naphthalene per 100 moles of Solvent, moles
Water	HOH	0.003	0.0004
Methanol	CH_3OH	8.2	2.1
Ethanol	CH_3CH_2OH	9.8	3.5
Acetic acid	CH_3COOH	13	6.1
n-Hexane	$CH_3(CH_2)_4CH_3$	14	9.4
Propionic acid	CH_3CH_2COOH	23	13.3
Isovaleric acid	$(CH_3)_2CHCH_2COOH$	17	13.5
Butyric acid	$CH_3CH_2CH_2COOH$	22	15.1
Aniline	$C_6H_5NH_2$	24	18
Toluene	$C_6H_5CH_3$	28	20
Carbon disulfide	CS_2	36	21.0
Benzene	C_6H_6	36	22
Carbon tetrachloride	CCl_4	20	24.0
Acetone	CH_3COCH_3	54	24.0
Chlorobenzene	C_6H_5Cl	31	27
Chloroform	$CHCl_3$	31	29.0
Nitrobenzene	$C_6H_5NO_2$	36	35

than gram solubilities. It may be noted that solubility is very low in water, low in alcohols, better in acids, and still better in carbon disulfide, acetone, halogenated hydrocarbons, and aromatic compounds. Thus the best solubility relationships are shown by compounds related structurally to naphthalene, that is, aromatic compounds. In general, halogenated hydrocarbons are good solvents for covalent compounds. Acetone is noted for its high solvent power. Acids are better solvents for hydrocarbons than are alcohols, for, although the oxygen content is higher, acids are known to be associated.

Organic solids of high oxygen content, for example glucose $C_6H_{12}O_6$, usually are insoluble in hydrocarbons, ethers, and halogenated hydrocarbons, slightly soluble in acids, more soluble in alcohol, soluble in water. In general the solubility relationships are the reverse of those of naphthalene. Organic liquids of high oxygen content, for example glycol $C_2H_4O_2$, show somewhat similar relationships except that they are miscible with many organic liquids, especially alcohols and acids, owing to mutual solubilities.

2.22 Effect of Molecular Weight. In any homologous series, the solubility of the high members in any one solvent approaches that of the corresponding hydrocarbons. This point is well illustrated in the

solubility of the normal primary alcohols in water. The lower members, methyl, ethyl, and propyl alcohols, are miscible in all proportions with water and thus are directly opposite in behavior to the hydrocarbons having the same number of carbon atoms. The fourth member, n-butyl alcohol, is soluble 8.6 g. per 100 g. of water, the fifth, n-amyl alcohol 2.7, and succeeding members continually less so until for the ninth member, n-nonyl alcohol, 0.088 is the solubility. Higher alcohols are even less soluble. Thus, as the hydrocarbon chain is increased, the properties approach those of the corresponding hydrocarbon as far as solubility in water is concerned. As the solubility in water decreases, the solubility in hydrocarbons increases. Thus, methanol, the first member of the series, is not miscible with kerosene, but anhydrous ethanol and higher members are miscible. Similar relations hold in the case of other homologous series, such as the acids.

2.23 Effect of High Oxygen or Nitrogen Content. Organic substances of high oxygen or nitrogen content usually dissolve in solvents of high oxygen or nitrogen content. Thus, those organic compounds that have a high oxygen content, for example the simple alcohols, acids, aldehydes, and ketones, in which the molecule has not more than three carbon atoms, are miscible with water. Even in more complicated molecules, for example glucose $C_6H_{12}O_6$ and sucrose $C_{12}H_{22}O_{11}$, the high oxygen-to-carbon ratio imparts high solubility in water. When the nitrogen-to-carbon ratio is high, the compound may be very soluble in water, as well as in nitrogen-containing solvents. Thus, cadaverine $(CH_2)_5(NH_2)_2$, is very soluble in water, in liquid ammonia, and in organic solvents.

2.24 Effect of Melting Point. Of two organic compounds that are alike in molecular weight and functional groups, but differ only in melting point, in general, the one having the lower melting point has the higher solubility in all solvents. As an example, of the two isomeric acids of the structure, HOCOCH=CHCOOH maleic acid, m.p. 130°, is 110 times more soluble in water than fumaric acid, m.p. 284° (actual values are 79 and 0.7 g. per 100 g.). Substances of high melting point, with the exception of many salts, usually have low solubilities in most solvents. For example anthraquinone, m.p. 380°, is insoluble in water and only slightly soluble in alcohol and ether. Substances like starch and cellulose, which have such high melting points that they decompose on heating before the melting point is reached, are insoluble in all solvents.

2.25 Effect of the Dielectric Constant of the Solvent. Highly ionized substances usually are insoluble in solvents of low dielectric constant, and are dissolved only by solvents of high dielectric constant

(see Table 2–2, Dielectric Constants).   Thus sodium chloride is insoluble in hydrocarbons and in ethers, slightly soluble in methanol, more soluble in glycerol, and most soluble in water.   Likewise, sodium and potassium salts of the simpler organic acids usually are more soluble in water than in the nonpolar ethers and hydrocarbons.   Often they are more soluble in alcohols than in water.   This is due to the operation of the effect discussed under 2.21.   Similarly, hydrochlorides of organic bases are more soluble in water than in ethers and hydrocarbons and often are more soluble in alcohols than in water.

TABLE 2–2

DIELECTRIC CONSTANTS OF SOME SOLVENTS AT CA. 20°

Hydrogen cyanide	116	Acetic acid	9.7
Formamide	84	Ethyl acetate	6.5
Sulfuric acid	84	Toluene	5.8
Water	81	Bromobenzene	5.2
Methanol	35	Chloroform	5.2
Ethanol	25	Bromine	4.6
Ammonia (−34°)	25	Ethyl ether	4.4
Acetone	24	Carbon disulfide	2.6
Propanol	22	Tetrachloroethylene	2.5
Isobutyl alcohol	19	Benzene	2.3
Isoamyl alcohol	16	Carbon tetrachloride	2.2
Acetophenone	13	Hexane	1.9
Ethyl bromide	10		

SECTION 2.3   OTHER FACTORS AFFECTING SOLUBILITY

2.31   Temperature Coefficient of Solubility.   Usually solubilities of substances in liquids are affected by changes in temperature.   The solubilities of solids usually increase, those of gases usually decrease, whereas those of liquids sometimes increase, sometimes decrease.   A substance is said to have a **positive temperature coefficient** of solubility when the solubility increases with a rise in temperature and a **negative coefficient** of solubility when the solubility decreases with a rise in temperature.

In Figure 2–1 are shown the solubility curves of many of the common inorganic salts.   It may be noted that most of these have positive temperature coefficients.   Also some of the coefficients are quite large; others, as for example that of sodium chloride, are quite small.   The student may think it strange to find such a table in a manual dealing with organic chemistry, but it proves to be very useful in laboratory work, for often an inorganic salt is present in a reaction mixture, some-

times as a reactant, more often as product.   A knowledge of its solubility properties facilitates its removal from the mixture.

It is quite reasonable to expect that the heat effect will determine whether the solubility will increase or decrease with temperature,
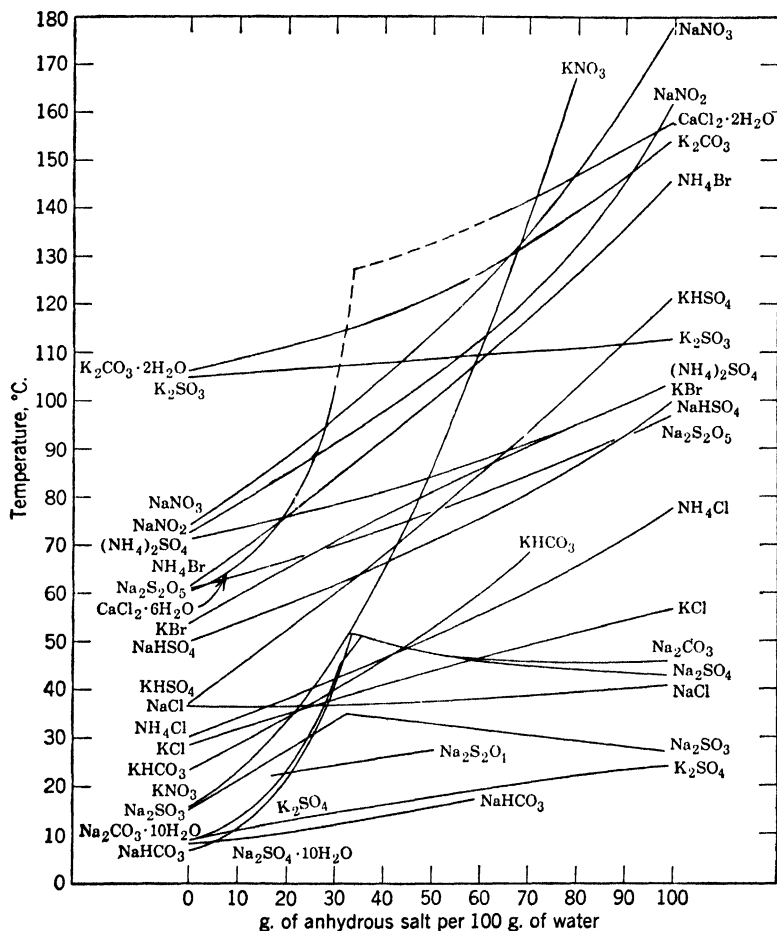

FIG. 2-1   Solubilities of Some Inorganic Salts in Water

according to the principle of Le Chatelier.   This is indeed true in the instance where heat is absorbed, for then the compound always has a positive temperature coefficient.   From a practical point of view, heat should be applied in this case to prevent the solution from becoming so cold that the solubility of the substance becomes small and its rate of solution becomes low.   When heat is evolved, it would appear logical

to assume that the temperature coefficient is negative. However, the heat effect may be due to solvation of the substance, that is, to a reaction with the solvent. In such case it is not possible to tell if all, none, or only a part of the heat evolved is due to the solvation. If none of the heat is due to solvation, the solid has a negative temperature coefficient, in accordance with the principle of Le Chatelier. If enough heat is due to solvation of the solute, the solubility increases even though heat is evolved.

2.32   State of Subdivision. Even at a given temperature the solubility may vary slightly with particle size, for fine particles are actually more soluble than coarse particles. From a practical viewpoint, use is made of this fact for the purpose of obtaining a coarser product from a finely divided solid precipitate by heating it, by agitating it with the solvent, or merely by allowing it to stand. Thus, the larger particles grow while the smaller ones dissolve. Discrepancies in solubility data arise in part from the slowness with which equilibrium is attained, and in part from variation in particle size.

2.33   Mutual Solubility of Liquids. A great many pairs of organic liquids are miscible with each other in all proportions. This is due to the mutual solubilities of the liquids in each other; that is, the extent to which one liquid dissolves in another liquid is of the same order of magnitude in moles as the extent to which the second liquid dissolves in the first liquid. Thus it is misleading to say that one liquid is infinitely soluble in another liquid, because the phenomenon of complete miscibility actually depends on mutual solubilities.
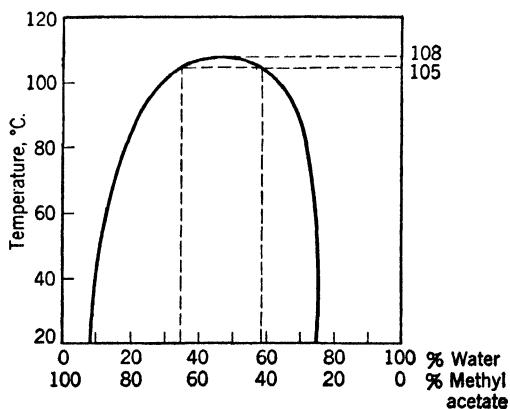

Fig. 2-2   Mutual Solubilities of Water and Methyl Acetate

The way complete miscibility of liquids depends on mutual solubility is illustrated in the water–methyl acetate system (Figure 2–2). Points

on the curve represent the composition of a liquid phase at the respective temperatures. Thus at 20° there are two liquid phases present, one containing 8.2% water, the other 75.8% water. The first is mainly methyl acetate; the second, water.

As the temperature rises, the solubility of each liquid in the other increases gradually. At 105° there is still a considerable difference in composition of the two phases, for one phase contains 34% water and the other phase contains 59.7% water. A small additional temperature rise of only 3° increases the mutual solubilities to the point where the two former phases have the same composition. Now only one phase results. Above 108° the two substances are miscible in all proportions. The system must be studied under pressure; otherwise, the compounds volatilize.

SECTION 2.4 DETERMINATION OF SOLUBILITIES

The accurate determination of the solubility of a pure solid in a liquid involves the preparation of a saturated solution of the solid in the liquid and the determination of the composition of this solution. In the preparation of such a solution, which is defined as one that is in equilibrium with the solid, it usually is necessary to agitate the finely divided solid with the liquid for a long time because the rate of solution becomes very slow as saturation is approached. The equilibrium may be approached from the opposite side by seeding a supersaturated solution.

In case two liquid phases result when two liquids are shaken together, the solubility of one in the other may be obtained in an analogous fashion. Since the rate of solution is comparatively rapid when the two are vigorously stirred, the equilibrium can be attained in a relatively short time.

The determination of the approximate solubility of a substance in a liquid can be carried out in a test tube by observing the disappearance of the solid as described in Experiment 2-1. It is important that the substance, if a solid, be in a **fine state of subdivision,** for the rate of solution depends on the surface area. Also, it is important to add the solid in portions and not all at once; otherwise, the finer material dissolves first, and only the coarser material remains as the solution approaches saturation. The amount that has gone into solution usually can be approximated fairly well, if the weight added is known and the amount undissolved is estimated, after saturation has been approximated.

The expressions *insoluble* and *slightly soluble* have no fixed meanings. The word *soluble*, as it is customarily used in organic chemistry, has come to mean a solubility of 5 g. or more per 100 g. of solvent. For

practical work in this course, a substance is considered insoluble if its saturated solution contains *ca.* 0.5% or less of the dissolved substance, and slightly soluble if it contains between *ca.* 0.5 and 5%.

Experiment 2–1   Solubilities in Water, Kerosene, and Methanol (Note 1)

Solubility tests should be carried out in such a way that one can decide if a substance is essentially insoluble (less than *ca.* 0.5%), slightly soluble (up to about 5%), or readily soluble in a given solvent, hot or cold.

To a given amount of solvent, 1 to 2 ml. in a small test tube or homeopathic vial, add a few milligrams of the solid in a finely divided condition. If the material fails to dissolve on agitation or after standing for some time with occasional agitation, it may be considered insoluble. If shaken vigorously the material may be distributed on the walls of the tube above the liquid and lead to a wrong conclusion. Heat the tube and contents by means of a small flame, and note if any of the solid has dissolved (*Caution:* Note 2). If it has, keep adding the finely ground material in small amounts until no more dissolves. From the amount taken, judge if the material is slightly soluble or readily soluble hot. If the solubility is low in the cold solvent and much greater in the hot, cool the hot solution, shake, and note if crystals separate. Could a purification of the original material be effected by this process? Explain.

If the original small amount of solid dissolved in the cold liquid, then more should be added until saturation is approached, it being remembered always that, the more finely divided the solid, the faster the rate of dissolving. After the saturation point is reached cold, the change in solubility on heating can be determined by the procedure mentioned in the preceding paragraph. It is thus possible to determine in a few minutes the approximate solubility of a solid in several liquids. In the case of colored compounds the extent of the color change in the liquid is useful, provided the color is not too intense. Note if crystals separate when the hot solution cools.

To determine the solubility of one liquid in another, add to 1 to 2 ml. of the second liquid a *small* drop of the first and shake (Note 3). If the resulting liquid is clear and only one phase is present, solution has taken place; otherwise not. However, one must not misinterpret slight emulsions which might be due to the presence of a third liquid soluble in the first and very insoluble in the second. If the first drop dissolved, add more of the liquid, drop by drop, until the limit of its solubility is reached. If the two liquids are miscible in equal proportions, they are probably miscible in all proportions.

Determine the solubility in water (b.p. 100°), kerosene (b.p. 200–300°), and methanol (b.p. 64.5°) of several inorganic substances such as calcium chloride $CaCl_2$, copper sulfate $CuSO_4 \cdot 5H_2O$, potassium permanganate $KMnO_4$, sodium acetate CH_3COONa, sodium hydroxide $NaOH$, sodium sulfate Na_2SO_4, concentrated sulfuric acid H_2SO_4, and of several organic substances such as acetone $(CH_3)_2CO$, benzoic acid C_6H_5COOH, carbon tetrachloride CCl_4, cottonseed oil, ether $(C_2H_5)_2O$, gasoline, glycerol $C_3H_8O_3$, naphthalene $C_{10}H_8$, oxalic acid $(COOH)_2 \cdot 2H_2O$, paraffin, sucrose (cane sugar) $C_{12}H_{22}O_{11}$, and urea $(NH_2)_2CO$.   Determine also the solubilities of the three solvents in each other.

Rate the solvents in the order of their solvent power for inorganic compounds.   This order illustrates well the solvent power toward salts. Do the same for the organic compounds.   This illustrates in general the solvent power of these three solvents for organic compounds.

Notes

1. Three students may cooperate in carrying out this experiment; one may determine the solubilities in water, another in methanol, and the third in kerosene. However, it is expected that each student will watch the experiments of the other two, so that he will be familiar with all the tests.   It is recommended that before the experiment is begun a table be made in the notebook incorporating the formulas of the compounds and so constructed that the results, as they are obtained, may be recorded in a neat and concise fashion.   Due acknowledgment must be made to others in the notebook in case any results are not one's own.

2. *Caution.* Use a *low flame*, and heat carefully so that the vapor does not come out of the tube; otherwise the vapor of kerosene may take fire.   Use a microburner or the base of a Bunsen (or Tirrill) burner from which the barrel has been removed.

3. In order to obtain small drops, allow the liquid to flow from a glass tube drawn down to a diameter of 1 or 2 mm.

Questions

1. Make a list of the compounds that are readily soluble in water.   Are they readily soluble in kerosene?

2. Make a list of the compounds that are readily soluble in kerosene.   Are they readily soluble in water?

3. Can similar statements be made about water and alcohol, or kerosene and alcohol?   Explain.

4. Is there any relationship between the solubilities of the carbon compounds in water and the ratios of oxygen to carbon in the compounds?

5. Which solvent would you select in order to purify by crystallization: sodium acetate, benzoic acid, naphthalene, oxalic acid, urea?   Give the reason for your choice.

6. What is the sign of the free-energy change when a solid dissolves in a liquid?

7. Show how, from free energy values of Table 1–3, it is possible to decide whether benzoic acid is liquid or solid at 25° and 1 atmosphere; also, whether its solubility in water at 25° is greater or less than 1 M.

Chapter 3

CALIBRATION OF THERMOMETERS

Thermometers are instruments for measuring temperature. The most common thermometers are those which make use of the fact that liquids expand as the temperature rises. Mercury (m.p. $-38.9°$, b.p. $356.9°$C.) thermometers are used ordinarily for measuring temperatures above *ca.* $-38°$, and pentane (b.p. $36°$) for temperatures below $35°$C. The upper range of the ordinary mercury thermometer is about $360°$C. If the thermometer is constructed of heavy glass tubing, so as to withstand the high pressure, it is possible to measure temperatures up to *ca.* $450°$ by means of mercury.

Chemical thermometers differ in accuracy. The best are calibrated according to exact specification, as, for example, the specifications of the U. S. Bureau of Standards. The maximum tolerance of such precision thermometers is $0.5°$ up to $100°$, and $1.0°$ up to $250°$. Ordinary chemical thermometers usually are fairly accurate at $0°$ and $100°$, but at other points the accuracy usually is less than that of precision thermometers. Sometimes they are in error as much as $3°$, or even $5°$. On this account recalibration is desirable.

Because mercury and glass have different coefficients of expansion, the height of the mercury thread, at a given bulb temperature, varies somewhat with the temperature of the mercury column. A thermometer, therefore, is calibrated if possible under conditions similar to those obtaining when it is in use. This is easily done if the thermometer is to be used at total immersion (entire mercury thread at bulb temperature) or at some standard immersion length (for example 3-inch immersion). If, however, the thermometer is to be used at various immersion depths, as in organic laboratory work, the best procedure is calibration at total immersion and application of a correction for the emergent stem.

When calibration is made at 3-inch immersion, only the lower 3 inches of the thermometer is kept at the calibrating temperature. Thermometers so calibrated are used extensively in industrial laboratories in standardized distillation operations, since only the lower 3 inches of the thermometer is within the distillation flask. Thus the temperature recorded by the thermometer is the temperature within the flask.

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When calibration is made at total immersion, the entire mercury thread is kept at the bulb temperature until the reading reaches a constant value.

SECTION 3.1 TEMPERATURES FOR CALIBRATION

The thermometer may be calibrated by determining its reading at known temperatures. The known temperatures may be obtained from a standard thermometer or from the transition points of pure substances, as for example in solid–liquid systems and in liquid–vapor systems.

3.11 Solid–Liquid System. The most useful of these is the ice–water system, 0°C. Others sometimes used are the solid–liquid systems of naphthalene, 80.8°, and benzoic acid, 122.5°.

Errors are introduced if the system is not at equilibrium or when impurities soluble in the liquid phase are present. The maintenance of equilibrium can be accomplished only by vigorous agitation. If the equilibrium temperature differs markedly from that of the surroundings, heat exchange occurs usually between the liquid and the surroundings. The temperature of the liquid rises above or falls below the equilibrium temperature. The only way it can be brought back to the equilibrium temperature is by contact with the solid. When a soluble impurity is present, the temperature of the system drops below the melting point, as discussed in Chapter 4. Pressure effects can be disregarded, as pointed out in Chapter 4.

3.12 Liquid–Vapor System. Many such systems are available, as for example benzene, 80.0°; water, 100.00°; aniline, 184.51°; naphthalene, 217.96°; biphenyl, 254.9°; and benzophenone, 305.9°.

Errors are introduced if the system is not at equilibrium, if the pressure gradient is appreciable, if air is present in the vapor, or if impurities are present in the liquid that bathes the thermometer. The equilibrium system is located on the thermometer itself, which is the most important region and the spot on which attention should be focused. Since boiling liquids are always superheated (Chapter 7), the thermometer should not touch the boiling liquid but should be suspended in the space above it; otherwise the reading may be high. Vigorous boiling usually is to be avoided, for it may lead to excessive pressure and to superheating the vapor, and this in turn may result in a dry bulb. Naturally, the thermometer reading will be high if the bulb is dry, and the temperature determination will be in error if the pressure of the vapor is different from the recorded barometric pressure. Impurities in the equilibrium system will alter the equilibrium temperature. In some cases it may be raised; in others, lowered (see Question 5, Experiment 3–1).

3.13   Correction for Barometric Pressure. If barometric pressure is not 760 mm., correction must be applied. This correction varies with the nature of the liquid and with the temperature. When the pressure is not far from 760 mm., the correction for a difference of 10 mm. in the pressure may be found by dividing the temperature of the boiling point on the **absolute** scale by certain factors. The factor is 1020 for associating liquids and 850 for nonassociating liquids.

SECTION 3.2   CORRECTION FOR EMERGENT STEM

When a thermometer which has been calibrated at total immersion is being used with a part of the mercury thread outside of the vessel, a correction, calculated according to Equation 3–1, must be applied.

$$C = +Kl(T_o - T_m) \tag{3-1}$$

where C = correction for exposed thread
$\quad\quad l$ = length of exposed thread in degrees
$\quad\, T_o$ = observed temperature
$\quad T_m$ = median temperature of emergent thread
$\quad\, K$ = 0.00016 = apparent coefficient of expansion of mercury in glass

The correction C is approximate because of the difficulty of determining the average temperature of the emergent thread of mercury. Even though the temperature of the air surrounding the upper part of the thermometer can be determined, that of the mercury thread may be different. The value of K varies; for normal glass it is 0.000158 at 0° and 0.000164 at 300°; for borosilicate glass it is 0.000164 at 100° and 0.000174 at 300°.

Experiment 3–1   Calibration of Thermometer (Note 1)

To calibrate the thermometer at 0°, fill a 100-ml. beaker with finely chopped ice, and add distilled water until it reaches to within about 2 cm. of the surface of the ice. Insert the thermometer into the mixture of ice and water until the zero point is just above the surface. Take the reading as soon as the thread becomes stationary. In order to avoid parallax the eye must be on a level with the top of the mercury column.

To calibrate the thermometer at a higher temperature by means of the vapor of a boiling liquid, attach a piece of clean *dry* glass tubing about 40 cm. long and 25 to 30 mm. in diameter (Note 2) to a clean dry 35-mm. test tube or to a Soxhlet wide-neck boiling flask by means of a

closely fitted unused cork stopper (not rubber stopper, Notes 3 and 4). Support the vessel by means of a clamp, place in it 25 to 50 ml. of the liquid to be used (Note 5), attach a cotton thread to the thermometer, lower it through the condenser tube until the bulb is about 10 cm. above the liquid, and support the thermometer by tying the upper end of the thread around the small piece of glass rod placed across the upper end of the condenser tube. Boil the liquid, but not so vigorously that large amounts of vapor escape (*Caution:* Note 6).

As soon as the vapor of the boiling liquid ascends above the height of the mercury column, take readings at intervals of about ½ minute until a fairly constant reading is obtained (Note 1). Liquid must always be observable on the thermometer bulb. Since many organic compounds decompose slowly at the boiling temperature, carry out the operations without needless delay. Record the barometric pressure, and correct the observed readings to 760 mm. (Note 7).

Calculate the temperature corrections that must be applied to the thermometer readings at the different temperatures. Draw a curve from which you can read the correction for any temperature. After answering the questions and completing the write-up in your notebook, report to the instructor before proceeding with the next experiment.

Notes

1. Enter all data in the notebook in a neat table, and figure out beforehand the number of columns needed, such as time, reading, barometric correction, and corrected temperature. The instructor may be consulted.

2. The thermometer is more easily held away from this condenser tube if the latter has three or four indentations at the same level.

3. Three students may cooperate here, each one calibrating the thermometers for all three at one temperature. Do not use the same cork stopper for different liquids, because the cork absorbs the liquids, and the absorbed liquids will contaminate each other.

4. It is important in drilling and fitting cork stoppers to follow a definite procedure for obtaining a well-bored well-fitting stopper. Select a cork that *barely* enters the neck of the flask, and soften it by rolling it under pressure, gently at first and more firmly as it begins to soften. Now the stopper should be soft. About one third to one half of it should enter the neck, and this part should fit tightly all the way.

To drill the hole use a sharp cork borer which is slightly smaller than the glass tubing (or thermometer). If it does not have a sharp edge, sharpen it with a cork-borer sharpener or, if this is not available, with files. Set the stopper on a rubber pad (the borer is dulled if bored into wood), and start boring the cork at the small end with *light* pressure. If the pressure is heavy, the side wall of the hole is not smooth. If the borer does not seem to grip, withdraw it and punch out the column of cork inside. The wall of the hole should appear smooth. Enlarge the hole with a round file if it is not large enough and fire-polish the glass tubing before inserting it.

Never insert sharp glass tubing into the cork opening. The wall of the opening becomes so badly cut that it will leak, sometimes quite badly.

5. The temperatures to be established should be distributed along the stem, at intervals not greater than 100°. For this experiment satisfactory temperatures are: 100°, 184.5°, and 218.0°, the respective boiling points of water, aniline, and naphthalene. It is desirable to lose some of the vapor in case a more volatile impurity is present.

It is important that the compounds be pure; otherwise the boiling points will deviate from the correct values. If the aniline is brown, it must be redistilled, and the first part of the distillate should be rejected since it usually contains a small amount of water. The organic compounds are not thrown away but are placed in bottles marked "residue."

6. Aniline vapor is poisonous.

7. Refer to the discussion.

Questions

1. Explain how vigorous boiling may cause the pressure in the flask to rise considerably above atmospheric.

2. Why is it desirable to have the entire mercury column surrounded by the vapor of the boiling substance?

3. Why must liquid always be observable on the thermometer bulb?

4. What is a nonassociating liquid? Associating?

5. Under the conditions of the experiment, how would the thermometer readings at 0° and 100° be affected if there were present about 5% of (a) sodium chloride, (b) ammonia, (c) hydrochloric acid, (d) mercury, (e) toluene? Would continued vigorous heating at 100° overcome errors due to any of these at 100°?

6. State clearly what errors would be involved at 180° if the apparatus contained moisture.

7. What disadvantages are inherent in the use of a thermometer calibrated at 3-inch immersion?

Chapter 4

MELTING POINTS

The melting point of a substance is the temperature at which the liquid and solid phases are in equilibrium. It is the temperature at which transition from one phase to the other takes place. The melting temperature of a pure substance does not change from the first appearance of liquid to the disappearance of the last trace of solid, provided equilibrium conditions are maintained during this time and provided that the substance does not decompose. The melting point is an important physical constant of a solid because it is an excellent criterion of purity, is easily determined, and is useful in the identification of the compound. A knowledge of the melting point of a substance being prepared in the laboratory is of value, in order for one to be ready to handle a liquid or a solid. Therefore the factors that affect the value of a melting point and the methods by which melting points are determined are important in organic laboratory work.

SECTION 4.1 FACTORS AFFECTING MELTING POINTS

4.11 Effect of Impurities. An impurity that is soluble in the fused substance lowers the melting point of the solid, and the mixture of the solid and impurity does not melt sharply, as a pure substance does, but exhibits a melting point range. The solid clumps together or softens, at a temperature much below the real melting point, and the actual melting process, with liquid present, occurs over a range of temperature. The temperature lowering is so pronounced in some cases that two low melting solids when mixed together, will liquefy, as shown in the case of the phenol–thymol system. An impurity that is insoluble in the fused substance does not alter the melting point but does cause the liquid to be cloudy.

THE PHENOL–THYMOL SYSTEM. Phenol (m.p. 39.5°) dissolves in fused thymol (m.p. 49.2°), and thymol dissolves in fused phenol. Each compound therefore acts as an impurity which lowers the melting point of the other. Figure 4–1 shows the extent of these effects. At room temperature the two solids yield liquid mixtures over the composition range of approximately 30 to 60% phenol. The lowest melting tempera-

ture for a mixture of phenol and thymol is 7.49°, composition 52% phenol, 48% thymol.

In the phase diagram (Figure 4–1) every point in the region labeled liquid which is bounded by solid lines (field A) represents a liquid of a composition and temperature corresponding to its position, that is, a liquid solution of one solid in the other. Every point in field B represents a mixture of pure solid phenol and a liquid composed of phenol and thymol, and in field C a mixture of pure thymol and a liquid composed

Field A. One phase: liquid mixture of phenol and thymol
Field B. Two phases: solid, phenol; liquid, phenol – thymol
Field C. Two phases: solid, thymol; liquid, phenol – thymol
Field D. Two phases: solid phenol and solid thymol
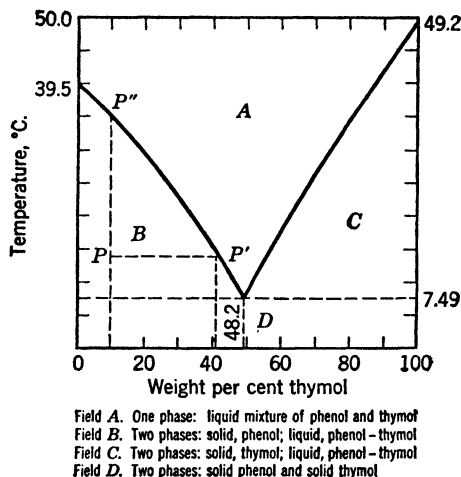
FIG. 4–1   Melting-Point Curve of Phenol–Thymol Mixtures

of phenol and thymol. Field D is the region of solid, where phenol and thymol exist as solids, at any temperature below 7.49°.

If heat is applied at 0° to a solid mixture consisting of 10% thymol and 90% phenol, the changes that take place can be predicted from Figure 4–1 if it is assumed that equilibrium between the phases is maintained at all times. There is no change until the temperature 7.49° is reached. Here a slight amount of liquid, composition 48% thymol is formed, and the amount increases while the temperature remains constant at 7.49° until all of the thymol has gone into the liquid phase along with the relative amount of phenol to maintain the liquid composition. Then, with further rise in temperature, more solid phenol melts, and the liquid becomes progressively richer in phenol. When the temperature reaches the point P, which is in the region of solid phenol plus a liquid mixture of phenol and thymol, the liquid has a composition of 59% phenol corresponding to the point P'. The liquid of that composition is in equilibrium with solid phenol at that temperature. Then on further

increase of the temperature more solid phenol melts, and the composition of the liquid in equilibrium with the solid moves up on the melting-point curve until the point P'' is reached. At this temperature, 35°, the last of the solid disappears, and only a liquid remains. Owing to the presence of 10% thymol in the phenol, therefore, there has been a melting range of 7.49° to 35° and a final melting point of 35°, which is lower than 39.5°, the melting point of pure solid phenol.

If in the original solid mixture the percentage of thymol is above 48, the melting temperature follows the right-hand solid curve. The final melting point is somewhat lower than 49.2°, depending on the original amount of thymol.

THE EUTECTIC MIXTURE. This is the composition of the mixture where the two curves intersect. It is the lowest melting mixture and has the property of melting at a constant temperature just as though it were a pure compound. On this account a eutectic mixture may be mistaken for a pure compound. Also, the composition of the eutectic corresponds to that of the first liquid that forms when any solid mixture of phenol and thymol is melted and to the last solid that forms when a liquid mixture of phenol and thymol solidifies.

Generally speaking, two organic solids, if miscible when in the fused state, have melting-point curves in which there is one minimum, as in the case of phenol and thymol. Sometimes there may be more than one minimum, because of a reaction between the two solids to form an addition compound, usually of relatively low stability, as for example a racemate. The occurrence of such an addition compound may cause the melting points of certain mixtures of compounds to be higher than the melting points of either pure compound. Increased melting points may result also from the formation of a solid solution.

FREEZING POINT LOWERING. Quantitatively the freezing-point lowering, ΔT, caused by a small amount of an impurity is given by Equation 4–1:

$$\Delta T = \mathbf{N}\, RT_o^2/\Delta H \tag{4-1}$$

where T_o is the melting temperature of the pure solid on the absolute scale, $\mathbf{N}$ is the mole fraction of the impurity, R is the gas constant, and ΔH is the change of heat content of a mole of the solid by fusing (the **molal heat of fusion**). Here R and ΔH must be expressed in the same units. Equation 4–2 is a simplified and more generally useful form which holds for dilute solutions.

$$\Delta T = 1000\, K_F w/WM \tag{4-2}$$

Here w and W are the weights of the solute and solvent, respectively; M is the molecular weight of the solute, and K_F is a constant, the **molal freezing-point lowering,** which is characteristic of the solvent. It is the temperature decrease produced by 1 g. mole of the solute in 1000 g. of solvent. Some molal freezing-point lowerings are listed in Table 4-1.

TABLE 4-1

MOLAL FREEZING-POINT LOWERINGS, K_F, AND HEATS OF FUSION

	Freezing Point, °C.	K_F	Heat of Fusion cal./g.	kcal./mole
Acetic acid	16.7	3.9	43.2	2.59
Benzene	5.5	5.12	30.1	2.35
Biphenyl	70.0	8.0	28.8	4.45
p-Bromotoluene	27.6	8.6	20.9	3.57
Camphor	178.4	37.7	10.74	1.63
Cyclohexane	6.5	20.0	7.4	0.62
p-Dibromobenzene	86.0	12.3	20.5	4.83
Ethylene bromide	9.98	12.5	13.5	2.54
Naphthalene	80.2	6.9	36.0	4.6
β-Naphthol	122.5	11.25	31.3	4.5
Nitrobenzene	5.7	8.1	22.46	2.7
Phenol	42.0	7.27	29.0	2.73
Water	0.0	1.86	79.67	1.43

Equation 4-2 is useful in calculating, from freezing-point lowering, the amount of dissolved impurity or the molecular weight of a dissolved substance. If the impurity is known, w/W can be calculated from ΔT, as in Experiment 20-4. If the amount dissolved is known, then M can be calculated from ΔT. Solvents that have high values of K_F, as for example camphor, are especially valuable in the determination of molecular weights. With this substance as a solvent, the depression of the melting point can be determined by the micro-technique described in this chapter.

4.12 Effect of Pressure on Melting Point. Pressure is also a factor in the melting point of a substance although usually it is negligible. From the principle of Le Chatelier it can be seen that the effect of pressure depends on whether the substance expands or contracts on melting. If the substance contracts on melting the application of pressure would aid contraction. Hence, the solid would tend to liquefy, and thus the melting point would be lowered. Water is one of the few substances that show this behavior. Owing to atmospheric pressure ice melts 0.0075° lower than it would if only water vapor were above it.

SECTION 4.2 DETERMINATION OF MELTING POINTS ON A MACROSCALE

The melting point of a solid can be determined quite accurately by slowly melting several grams of the substance while a thermometer is immersed in the mixture. In order to have the solid and liquid phases in equilibrium, mixing must be thorough at all times. In this way it is possible to note the melting range, that is, the temperature from the time of initial melting to that of disappearance of the solid. This is important, for the temperature range is quite small when the substance is pure and is extensive if much impurity is present.

SECTION 4.3 DETERMINATION OF MELTING POINTS ON A MICROSCALE

Usually it is desirable to use a small amount of material. Often this is all that is available. Moreover, it is more convenient to work with a small sample, and it often is a saving of material where oxidation or decomposition takes place on heating.

A good way to determine the melting point of a solid is to place a small portion in a thin-walled capillary melting-point tube attached to the bulb of a thermometer suspended in some suitable liquid and to raise the temperature of the liquid until the solid melts; or the melting-point tube and the thermometer may be placed in a copper block equipped with a window through which the sample is observed. In another method the sample is placed between thin glass plates on top of a copper block heated from below. The success of any of these methods depends on having the thermometer record the temperature of the melting solid.

4.31 Melting-Point Tubes. These are made from clean and dry glass tubing, 10 to 15 mm. in diameter (or from ordinary test tubes), by heating in a hot flame and drawing down to a diameter of 1 to 2 mm. The glass must be heated until quite soft, drawn slowly for a short interval of time (½ to 1 second), then rapidly and in a straight line to the desired diameter. It is held taut for a few seconds while cooling and setting. If the glass is drawn rapidly at the start, the capillary usually will be too small. The section from which the melting-point tubes are made should be fairly long and should be straight; otherwise, the tubes will not adhere well to the thermometer.

The long section is made into tubes 60 to 80 mm. long by cutting at one end and fusing off the other end. If they are cut at both ends and then later fused at one end in a flame, moisture will enter from the flame. This is undesirable, for the moisture may act as an impurity and

cause a lowering of the melting point of the substance. It is a good plan to make quite a number of tubes, which can be stored in a stoppered bottle or test tube and used as needed. They should be straight, and the walls should be thin. If the tubes are curved, they will not adhere well to the thermometer, and, if the walls are thick, the lag due to slowness of heat transfer may lead to a high value of the melting point.

4.32   Preparation of the Sample. The solid must be perfectly dry to give the correct melting point. For research purposes drying usually is done at 50° or 60° under reduced pressure, but for ordinary work it is sufficient to spread with a spatula a small amount (0.1 to 0.2 g.) of the solid thinly and firmly on a highly adsorbing material, as, for example, porous tile. It is allowed to remain for some time and is respread once or twice. Care must be taken, however, not to remove the rough surface of the porous tile by scraping and thus get it mixed with the solid. The porous tile adsorbs moisture and liquid impurities. The material should be in a fine state of subdivision for two reasons: (1) to obtain good contact with the porous surface, (2) to facilitate its introduction into the tube later.

4.33   Filling the Melting-Point Tube. The tube is inverted over the solid and pressed into it gently a few times. The material caught at the top may be made to fall to the bottom in different ways. The simplest is rubbing the side of the tube with a file. If not packed too firmly, the solid will be loosened by the vibration and will drop to the bottom. If this does not work, the tube is held vertically between the thumb and first finger, and the hand is struck against the desk. Or the tube may be dropped down a 2-foot length of glass tubing onto the desk. The solid should be fairly well packed at the bottom and should extend for a distance of 1 to 3 mm. up the tube. In any event the amount should be such that it can be observed readily.

4.34   Heating the Sample. A liquid bath is generally used for heating the sample. The simplest liquid bath consists of a beaker (usually 100 ml.) of liquid set on a wire gauze 1 or 2 cm. above a small burner A (Figure 4–2) with a thermometer suspended in the liquid. The beaker is filled one-half to two-thirds full with some suitable liquid, which is stirred by an up-and-down motion of a circular stirrer, the handle of which is bent downwards so that it can be manipulated easily by the hand while the elbow rests on the desk top. The apparatus should be kept assembled, if convenient, since it will be used from time to time.

Other liquid baths are shown in Figure 4–2. In B, the double liquid bath gives fairly uniform heating. In the Thiele apparatus C, hot liquid rises in the outer arm, but, since there are large temperature gradients,

this apparatus is not satisfactory. In *D*, the melting-point tube is inserted through the side arm and rests against the thermometer. An advantage is ease of removal. Also there may be two or more side arms thus allowing two or more determinations with one heating.

Liquids that may be used are high boiling and stable, such as sulfuric acid, glycerol, cottonseed oil, paraffin oil, and butyl phthalate. Sulfuric acid is dangerous, for the liquid, especially when hot, is very corrosive
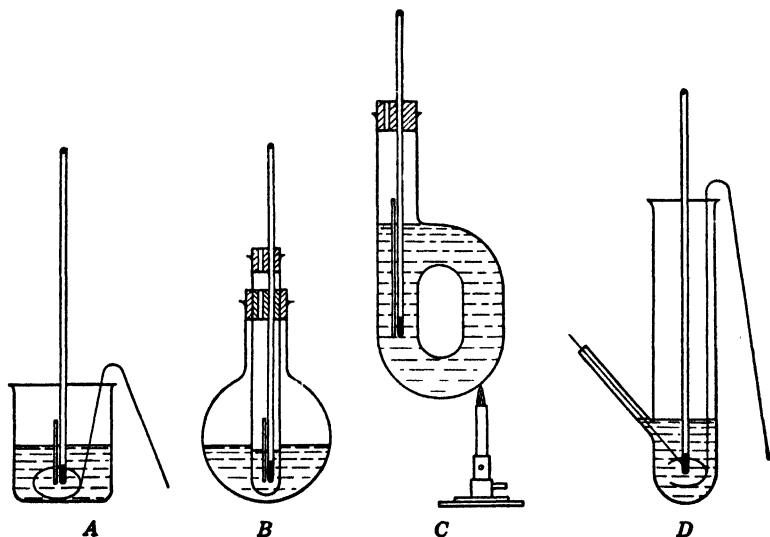

FIG. 4-2   Baths for Melting-Point Determination

to skin, clothing, desk, and so on. It is wise to wear spectacles or goggles. Paraffin oil, cottonseed oil, and butyl phthalate are more convenient, because they do not absorb moisture from the air on standing. They may be left in the apparatus, but sulfuric acid and glycerol must be removed before the apparatus is put away and saved in a stoppered bottle for future use. In any case the liquids should not be thrown away until they become dark colored.

4.35   Taking the Melting Point. The melting-point tube may be attached to the thermometer by a small tightly fitting rubber band cut from small rubber tubing. Adjustment should be made so that the sample is opposite the middle of the thermometer bulb. When a bath is used, the melting-point tube, if straight, will adhere to the thermometer by capillarity, so that a rubber band is not necessary. The thermometer is placed in the heating medium, heat is applied, and the tem-

perature is carried up rapidly, in case the melting point is not known, in order to obtain an approximate melting point.

To obtain an accurate value of the melting point, the bath is brought to a temperature about 10° below the approximate melting point, a second tube of the sample is attached to the thermometer, and then heat is applied at a *uniform* rate so that the temperature rises slowly, not faster than *1° per minute*. If the heating is too rapid, a decided range of melting will be noted, even if the compound is pure. The reason is that time has not been allowed for the transfer of a sufficient amount of heat through the insulating glass wall.

Three temperatures are recorded, namely, the point of first observable shrinkage, the point at which droplets begin to form, and the point at which the solid is completely liquefied. The first is the softening point. The second and third constitute the range of the melting point and should be recorded as the **observed melting point.** Under no circumstances should these two values be averaged and reported as the melting point. Next two corrections are applied, namely, the one obtained from the thermometer calibration, and the one for exposed mercury thread. The final value constitutes the **corrected melting point.**

4.36 Deductions to Be Drawn from the Melting Point. If the range of the melting point is greater than 1° or if softening occurs much below the melting point, impurities probably are present, it being assumed, of course, that the proper technique was employed during the determination. The substance should be purified by crystallization from a suitable solvent (Chapter 5) and the melting point redetermined. Should it now be higher, the operation is repeated until the melting point reaches a constant maximum value.

Experiment 4–1   Determination of Melting Points (Note 1)

Make up small quantities of three different mixtures of naphthalene $C_{10}H_8$ and p-dibromobenzene $C_6H_4Br_2$ by grinding together small amounts of each (Note 2). These mixtures should have approximate compositions as follows: A, 90% $C_{10}H_8$ and 10% $C_6H_4Br_2$; B, 50% of each; C, 10% $C_{10}H_8$ and 90% $C_6H_4Br_2$. Determine roughly the melting points of naphthalene, p-dibromobenzene, and the three mixtures. Record the data neatly in a table (Note 3). Note if the last three form one or two liquid phases on melting. Plot your results.

Determine with care the melting point of naphthalene and of an unknown (Note 4), and apply the proper corrections. After completing the write-up and answering the questions report to the instructor.

Notes

1. In order that the class may become familiar with various types of melting-point apparatus, it is desirable that a wide assortment be used.

2. For the sake of economy take into account the amount used in a single determination.

3. The following is recommended:

Substance	No.	Observed		Exposed Hg Thread		Corrections		Melting Point, °C. cor.
		Softn. Point, °C.	Melting Point, °C.	Avg. Temp., °C.	Length, °C.	Exposed Thread, °C.	Thermometer, °C.	
	1							
	2							
	3							

4. Obtain from the instructor.

Questions

1. Why is the temperature carried up rapidly in the preliminary heating and slowly in the second?

2. Which gives more accurate melting points, immersing the thermometer in a mixture of liquid and solid or using the capillary-tube method? Explain why.

3. How do you account for the fact that the mixtures of naphthalene and dibromobenzene melt at temperatures different from those of the pure compounds?

4. Supposing you had about 0.1 g. of an unknown organic substance melting at 79-80° and you suspected it to be naphthalene, how could you quickly determine if it were naphthalene or not?

5. If naphthalene were placed under high pressure and the melting point determined, would it be changed from the value at atmospheric pressure? Explain how the necessary information could be obtained from a simple test-tube experiment.

6. Calculate the pressure required to change the melting point of water by 0.1 °C.

Chapter 5

CRYSTALLIZATION AND FILTRATION

Solids usually are purified by crystallization from suitable solvents. In some cases the solvent may serve to dissolve the substance but not the impurity, which then is separated from the resulting solution by filtering or centrifuging. Usually, however, the solvent serves to keep the impurity in solution while the substance in question crystallizes out.

The crystallization of the solid from the liquid may be carried out by allowing the liquid to evaporate spontaneously or by decreasing the solubility of the solid in the liquid. This decrease in solvent power may be accomplished by the addition to the solution of another liquid which is miscible with the original solvent and in which the solid is much less soluble. However, the usual method of decreasing solvent power is to lower the temperature of the solution, since most solids have positive temperature coefficients of solubility.

If one operation does not yield a pure substance, the process is repeated, either with the same solvent, or with another, until the substance is pure, as shown by a melting-point determination. Naturally, there is some loss; however, it should be the aim of the manipulator to minimize loss, so as to obtain a good recovery of the solid.

SECTION 5.1   METHODS OF CRYSTALLIZATION

5.11   Crystallization by Spontaneous Evaporation. Although this method is useful for obtaining large crystals by the slow evaporation of pure solutions, in general it is not so valuable as other methods when the solution contains impurities. As the solvent evaporates, the concentration of any soluble impurity continually increases until it also may separate. Even before this point is reached, a crust of impure solid may form at the surface of the liquid. This contamination arises from the fact that a portion of the solution evaporates entirely, with resultant separation of other material besides the desired solid. However, where the change in solubility in the working temperature range is small, as, for example, in solutions in ethyl ether, slow evaporation may be the best procedure. Concentration by spontaneous evaporation when the

60

solvent is highly volatile should not be carried out rapidly as, for example, in an open vessel, because: (1) the fire hazard is too great; (2) moisture is condensed on the liquid, owing to cooling; (3) a crust is liable to form at the surface. Evaporation should be allowed to proceed slowly, preferably from a flask, the neck of which may be partially closed if desired, or from a beaker covered with a watch glass.

5.12   Addition of a Second Miscible Liquid. The solid separates, sometimes in a satisfactorily pure state, when it is not very soluble in the added solvent. However, often there are disadvantages to this procedure, for (1) the impurity also may come out of solution if its solubility is decreased at the same time; (2) the desired substance, especially if its melting point is not far above room temperature, may separate as a second oil phase; and (3) much of the desired compound may remain dissolved, owing to the fact that the total volume of the solution is increased.

5.13   Crystallization by Cooling a Solution. This is by all odds the best way to purify a solid by crystallization. It involves obtaining a clear, saturated, or nearly saturated solution of the solid, cooling the solution, collecting the solid by suction filtration, and removing the residual solvent from the solid. The solution usually is made in the boiling solvent, and this is the procedure followed in Experiment 5–1. The discussion that follows is concerned mainly with crystallization by cooling a solution.

SECTION 5.2   PREPARING THE SOLUTION

5.21   Selection of Solvent. In crystallization by cooling a hot solution, the solvent should possess certain characteristics, so that, in general, purification can be effected conveniently and with minimum loss: (1) The solvent should not boil at too low a temperature; (2) it should not boil at too high a temperature; (3) it should possess slight or at best moderate tendency to dissolve the solid at the temperature of crystallization; (4) it should dissolve the solid much better at elevated temperature; that is, the temperature coefficient of solubility of the solid in the liquid should be reasonably high.

If the boiling point is low, or if the solution is prepared at a temperature below *ca.* 50°, generally the change in solubility on cooling to about 20° is not sufficiently great. If the boiling point is too high, the solute may decompose. Moreover, complete removal of the solvent after filtration is difficult. However, this may be accomplished by washing the solid with a suitable more volatile solvent. If the solvent dissolves the solid readily at room temperature, much of the latter will be lost,

and the recovery will be low also. Cooling to a point below room temperature usually permits the use of a low-boiling solvent or of a solvent in which the solid is readily soluble at room temperature.

Sometimes, especially when the melting point of the solid is not much above room temperature, a low-boiling solvent is best. In such a case, a satisfactory temperature difference may be realized by cooling to 0° or lower in a freezing bath or in a refrigerator, or to −80° by Dry Ice. However, cooling below room temperature has the disadvantage that moisture from the air condenses on the cold solution and also on the cold solid as soon as they are exposed to the air. Care must be taken that the solute and not the solvent is the substance that crystallizes.

If one does not know beforehand which solvent to employ for the purpose of purifying a known impure solid, several solvents of intermediate solvent power should be selected in accordance with the solubility rules in Chapter 2. Some solvents commonly used in the crystallization of organic solids are listed in Table 5–1 along with their boiling

TABLE 5–1

SOME COMMON SOLVENTS

		B.P., °C.	M.P., °C.
Ethyl ether	$(C_2H_5)_2O$	35	−116
Petroleum ether	Pentane and hexane	40–60	
Acetone	$(CH_3)_2CO$	56	−95
Chloroform	$CHCl_3$	61	−63
Methanol	CH_3OH	65	−98
Isopropyl ether	$(i\text{-}C_3H_7)_2O$	68	< −80
Carbon tetrachloride	CCl_4	76	−23
Ethyl acetate	$CH_3COOC_2H_5$	77	−84
Ethyl alcohol	C_2H_5OH	78	−112
Benzene	C_6H_6	80	5.5
Ligroin	Mixture	80–100	
Isopropyl alcohol	$(CH_3)_2CHOH$	82	−86
Water	H_2O	100	0.0
Toluene	$C_6H_5CH_3$	111	−92
n-Butyl alcohol	$n\text{-}C_4H_9OH$	117	−80
Acetic acid (glacial)	CH_3COOH	118	16.7
m-Xylene	$C_6H_4(CH_3)_2$	139	−54
n-Butyl ether	$(n\text{-}C_4H_9)_2O$	142	−98
Nitrobenzene	$C_6H_5NO_2$	211	5.7

points and melting points. The approximate solubility of the substance in solvents, hot and cold, is determined according to the procedure followed in Experiment 2–1. Since the solid may be mixed with less

soluble material, one should be on the alert to observe changes in the appearance of the solid as solution takes place and not try to dissolve all the solid. In the preliminary tests it usually is not necessary to separate out any less soluble contaminant, in order to determine if material crystallizes on cooling.

5.22   Dissolving the Solid.   The material, preferably in a fine state of subdivision, is placed in a flask of suitable size. A reflux condenser is attached in case the solvent is not high boiling, some of the solvent is added, but an amount much less than that approximated by the preliminary tests, and the mixture is heated while being agitated.

The solid should be finely divided to aid dissolving, since the rate of solution depends on the interfacial area. Large particles often dissolve slowly, even when an excess of solvent is present.

A flask is preferred to an open dish, such as a beaker, because (1) the hot solvent evaporates too rapidly from an open vessel; (2) the fire hazard is too great in an open vessel because vapors of inflammable liquids are heavier than air and descend around the burner; (3) the vapor can be condensed and returned to the flask.

The amount of solvent first added should be about one fourth or one third of that estimated from preliminary tests, because such estimates invariably are much too high. If too much solvent is taken, the recovery of solid will be low; if too little, more can be added if some of the solid remains undissolved after the solvent has boiled for a few minutes. However, one should not confuse a slightly insoluble impurity with undissolved substance; otherwise, too much solvent may be added. It is well to remove the first portion of solvent before adding a second because the solid dissolves faster in fresh solvent. Moreover, the residual solid dissolves much more slowly than the original, since the finest particles have already dissolved. Thus, as the solid dissolves, the rate of solution diminishes for two reasons, namely: The solvent action of the solution continually becomes less, and the particles continually offer less and less surface.

The heating may be done by a small flame, by an electric heater, by steam, or by a liquid bath, such as water, or a nonvolatile oil. A small flame is used in order to decrease the fire hazard. An electric heater or a liquid bath minimizes the fire hazard, but control of the heat input is not so easy as with flame heating because of the reservoir capacity of the hot plate or the liquid bath. Steam heating is convenient when a temperature of 100° is desired. The time of heating should not be prolonged needlessly, because reactions sometimes take place, as for example decomposition.

5.23 Decolorizing. If the filtrate is colored by high-molecular-weight organic material, such as that resulting from decomposition, boiling with a suitable adsorbent form of carbon, a few grams per liter, usually will remove the color. Less carbon is required if added in several portions. The amount of carbon should be kept at a minimum, for some of the desired solid is adsorbed likewise. Norite and Nuchar are two commercial preparations that are quite effective.

Fluted paper, for hot liquids	Glass funnel with perforated plate	Porcelain funnel, Buechner	Porcelain funnel, Hirsch	Glass funnel with fritted glass plate
A	B	C	D	E

Test tube with side arm	Test tube in suction flask	Suction flask fitted with rubber plate	Trap
F	G	H	I
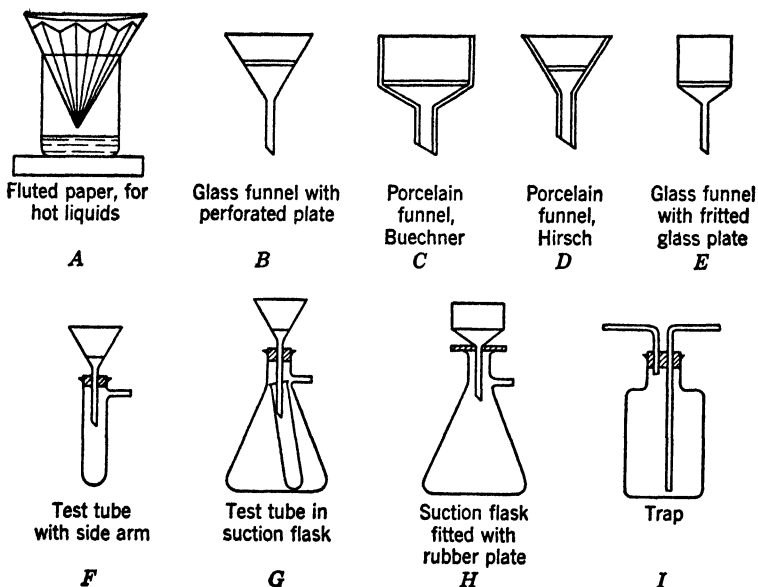
FIG. 5–1   Filtration Apparatus

5.24 Filtering the Hot Solution. The solution, which may be colored, must be filtered unless clear. This operation should be carried out so that the drop in temperature is kept to a minimum. If the cooling is considerable, solid may separate in the filter and in the stem of the funnel, with the result that the rate of filtering becomes quite slow, and much solid crystallizes in the wrong place. The principal precautions to take in order to prevent excessive cooling are (1) conducting the filtration as rapidly as possible, (2) heating the funnel and filter paper to the temperature of the boiling solution, and (3) reducing evaporation of the solvent to a minimum.

Rapid filtration of a hot volatile liquid may be achieved by different procedures: (1) gravity flow through a fluted filter paper in a glass funnel, preferably a stemless funnel set in a beaker (A, Figure 5–1);

(2) suction through a flat piece of filter paper on a perforated filter plate, as with a Witte plate B, a Buechner funnel C, or a Hirsch funnel D; or (3) suction through a porous plate, as, for example, a fritted glass plate E. In general, beginning students should follow method 1 because of the difficulties associated with methods 2 and 3, mainly clogging of the filter due to evaporation of the solvent. Figure 5–1 shows some types of apparatus used in suction filtration. The proper selection of filter paper is discussed in Section 5.5, and directions are given there for fluting filter papers and for properly placing these in the funnel.

The temperature of the filtering apparatus must not be much below that of the solution; otherwise, some of the solid will crystallize as soon as the liquid strikes the colder surface. When hot liquids are being filtered, there are different ways of avoiding this. When procedure 1 is followed, some of the pure solvent is placed in the beaker, the funnel is covered with a watch glass, the solvent is heated to boiling, preferably by means of an electric hot plate, until the entire apparatus is heated. The extra solvent is poured out just before filtration is begun. A modification is the use of a funnel with stem, set in a flask, so that the whole can be heated by boiling liquid in the flask. When procedures 2 or 3 are followed, the funnel and suction flask may be heated by pouring through the funnel some of the hot solvent or by passing steam into the stem of the suction flask and out at the funnel. This should not be done if the solvent is not water (*Caution:* the filter flask, unless made of Pyrex glass, may crack if heating is too sudden).

Evaporation of the hot solvent has two effects: (1) The solution becomes more concentrated, and (2) the solution becomes cooler. Both these effects lead to separation of solid. In general, evaporation is more troublesome when suction is used and, if the operation is carried out carelessly, may lead to the separation of much of the solid in the funnel. Evaporation is especially detrimental if it takes place in the filter paper, causing it to be clogged with the solid. This results from drawing air through the filter after the liquid has passed through. On this account, the filter should have liquid on it until the operation is complete. If solid separates in the suction flask, it may be redissolved, by replacement of the evaporated solvent and reheating.

5.25   Filter Aid. Oftentimes filtration becomes slow after a portion of the liquid has passed through, owing to the presence of colloidal or gelatinous material, which clogs the pores of the filter paper. Usually this difficulty can be remedied by adding directly to the liquid a filter aid, that is, a finely divided solid which adsorbs on its surface the undesirable colloidal material. Some form of siliceous earth is commonly used for this purpose, as for example Fuller's earth, kieselguhr, or

diatomaceous earth. An especially good variety of the last is "Hyflo," used extensively in industrial operations. The amount taken should be sufficient to form a layer at least 2 mm. thick on the filter.

If the solution is not clear, it must be refiltered until it is clear, while any changes in temperature or volume of solution are kept to a minimum.

SECTION 5.3 THE CRYSTALLIZATION PROCESS

5.31 Cooling a Hot Solution. If the preparation of the solution and the filtration are done properly, the filtrate is a hot clear solution, saturated or almost saturated with the desired solid. The solution should be allowed to cool with little or no loss of solvent, either in a covered beaker, or preferably in a covered flask. As the solution cools, crystals of the solid usually separate spontaneously, the size of the crystals depending on the rate of crystallization, small if the rate is rapid, larger if the rate is slow. The rate of crystallization depends on the degree of supersaturation and on the rate of cooling. If the liquid supercools considerably, the initial rate of crystallization is fairly high. Agitation, scratching, or, better, seeding with small crystals from time to time as the liquid cools, usually prevents excessive supersaturation. Since the particles of solid that separate are pure, any contamination of the dried material will come from the liquid that has not been removed from the solid. The less extensive the surface of the solid, the less will be the amount of liquid that wets it. On this account, it is better to allow the crystals to grow fairly large through slow crystallization than to obtain a fine crystal meal by rapid crystallization.

The mixture of liquid and crystals should be allowed to stand with occasional agitation until crystallization is complete. Almost invariably the time allowed for this by students is too short, because of the pronounced tendency of organic solids, especially those of high molecular weight, to form supersaturated solutions. On this account the filtrate obtained later (see 5.41) should always be set aside for observation.

5.32 Oil Formation. An oil may separate, especially if the solid is low melting. Oil formation actually is the separation of the solute in the fused state, and this may be a thermodynamically stable state, even though the temperature is below the freezing point of the solid, since the solvent lowers the freezing point of the solute. Even if the oil solidifies later, the material is contaminated, because it contains the impurities which had dissolved in the oil. The benzene–phenylenediamine system described in the following illustrates oil formation.

In Figure 5–2 are shown the curves that represent the nature of various mixtures of *m*-phenylenediamine (m.p. 62.8°) and benzene (m.p. 5.5°) at different temperatures. Field *A* is the region of a single-phase liquid.

At temperatures above 69.0° the two molten compounds are miscible in all proportions. Between 53.8° and 69.0° two liquid phases will exist when the composition of the mixture lies in the region of field B. One is m-phenylenediamine dissolved in benzene, and the other is benzene dissolved in m-phenylenediamine. Field C represents the region of solid phenylenediamine and the first liquid mentioned, and field D represents the region of solid phenylenediamine and the second liquid mentioned. The boundary curve of field C up to 53.8° represents the solubility of the solid in benzene, and the boundary curve of field D represents
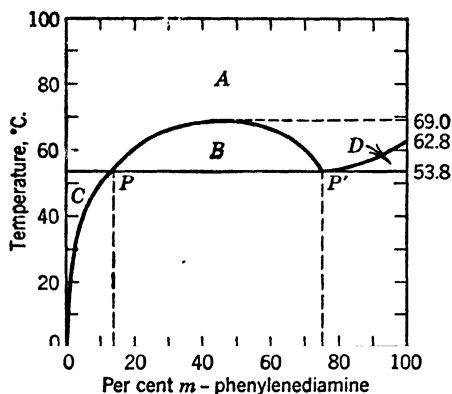
FIG. 5-2   System, Benzene-m-Phenylenediamine

the depression of the melting point of phenylenediamine by benzene. It is important to note that a solvent can cause a lowering in the melting point of a solid.

As benzene is added to solid m-phenylenediamine, the freezing point of the mixture drops to 53.8°, since benzene acts as an impurity (recall Figure 4-1). Addition of more benzene, with the temperature of the system above 53.8°, results in the formation of two liquid phases, until the percentage of benzene exceeds 82%, where at point P only one liquid phase exists. On cooling solutions containing up to 18% m-phenylenediamine (point P) below 53.8°, solid phenylenediamine will crystallize out. But on cooling any other hot solution which contains 18 to 75% dissolved solid, two liquid phases will first form, and at 53.8° they will have the compositions shown as P and P'. Additional cooling causes the separation of pure crystals from the former, and solidification of the latter with entrainment of much of the benzene present, along with any impurities that either might contain. On cooling the benzene solution to slightly below 5°, the eutectic temperature, solid benzene begins to separate. At this point only a fraction of a per cent of the

phenylenediamine remains dissolved. Only from solutions containing less phenylenediamine than corresponds to the eutectic mixture does pure benzene separate in crystalline form as the solution is cooled.

5.33   Overcoming Oil Formation. From the foregoing discussion, it can be seen that, when an oil separates as the solution is cooled, the situation can be remedied by dilution to 18% phenylenediamine, where crystals will form first. Even after dilution, over 90% of the phenylenediamine is recovered by cooling only to 20°.

In general, in other instances as well as with phenylenediamine, it is possible to avoid oil formation during crystallization by making use of one or more of the following procedures: (1) keeping the temperature of the solution below the melting point of the pure solid; (2) adding more solvent, if oil separates, until the oil dissolves; (3) allowing the temperature to drop slowly, adding a few seed crystals from time to time; (4) removing the initial small crop of impure solid which results when the oil solidifies.

SECTION 5.4   HANDLING THE SOLID

5.41   Collecting the Solid by Suction Filtration. The mother liquor is now removed from the crystals by suction filtration. Since the mother liquid contains the impurities, it is the aim of the suction treatment to *remove as much of the liquor as possible from the solid without evaporating the solvent.*

The funnel should be of such a size that a thick layer of solid will be obtained. This is preferred to a thin layer, because the mother liquor can be more completely removed without evaporation. The funnel should be thoroughly clean, especially on the inside, because it may be desirable to obtain a crop of crystals from the filtrate later. In some cases recovery of material from the filtrate is prevented completely by impurities picked up by the solvent. The paper should fit well and lie flat. It should be wet with solvent, and suction should be applied to insure that air does not leak past the edges. The funnel is fitted to the flask by means of a rubber (not cork) stopper or by a piece of sheet rubber about 3 inches square with a hole in the center for the funnel stem (*F*, *G*, and *H*, Figure 5–1).

The size of the suction flask should be commensurate with the volume of the mixture being handled (*F*, *G*, and *H*, Figure 5–1). It should not be connected directly to a water aspirator but should be protected by a trap to prevent water from being sucked back into the flask (*I*, Figure 5–1). This is so fitted that any water in the trap is removed when suction is applied.

The mixture of liquid and solid is thrown on the filter either with no suction or at best with only slight suction so as to avoid needless evaporation. The solid remaining in the flask is washed out by using some of the filtrate, rather than with pure solvent, to avoid solution of solid. When all the solid is on the filter, the suction is increased. Just as soon as the filter cake becomes firm enough it is carefully and firmly pressed with a flat object such as a small vial or an inverted bottle stopper, the object selected depending on the size of the filter cake. This is done almost continuously as long as any liquid flows. This operation serves to close the cracks which constantly form in the filter cake. If it is neglected, air rushes through the cracks, with resulting needless evaporation of the solvent and loss of vacuum. *The filter cake must be pressed continuously* so long as liquid comes through. *The suction must be discontinued as soon as no more liquid filters through,* the flask being disconnected first before the pump is turned off. When the solvent is very volatile, as for example ether, evaporation is especially extensive. However, this may be overcome by tying a diaphragm of sheet rubber, like that used for rubber dams, over the top of the funnel. Suction then draws the diaphragm (rubber dam) down on the solid rather than drawing air through.

A second crop of crystals often can be obtained from the filtrate. Some of the solvent, usually about one half or two thirds, is distilled or evaporated, and the process of crystallization is repeated. Since the impurities are concentrated at the same time, the second crop of crystals is less pure.

5.42 Washing the Solid. For washing the solid a satisfactory procedure is the following: (1) Break the suction; (2) transfer the filtrate to a flask; (3) add to the solid, either on the funnel or preferably in another vessel, enough of the cold solvent to form a pasty mass, and stir so as to get good contact; (4) apply suction as previously; (5) repeat if necessary.

The object of washing the solid is the removal of the residual mother liquor which wets the solid and which may constitute more than one half of the mass. If the solvent has evaporated during the filtration process, the impurity which dries onto the surface of the solid is not removed easily by the washing process.

5.43 Drying the Solid. Since the mother liquor usually is not completely removed by ordinary washing, and since the filter cake may be 50% solvent, as much of the residual solvent as possible should be removed by *absorption* rather than by evaporation.

The absorbing medium may be good absorbing paper, as for example filter paper, or it may be porous tile of good absorbing properties. The filter cake is removed by blowing into the stem of the funnel, inverted

over the absorbing medium. The solid should be pressed *firmly* between pieces of absorbing paper, the pieces being removed as soon as they become wet, or it should be pressed out in a *compact* mass onto porous tile.

After this treatment, a considerable amount of solvent still remains and can be removed by evaporation. This is accomplished by (1) exposing to air at room temperature; (2) heating in an open space. Exposure

A. Recommended for
general use

B. Scheibler type;
liable to breakage

C. Abderhalden Drying Pistol,
for heating solid while drying
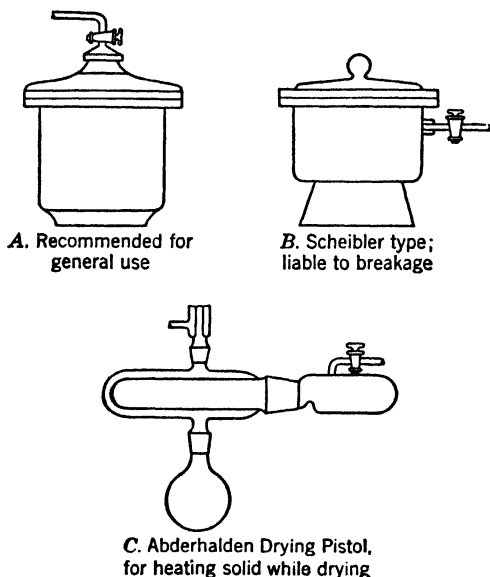
FIG. 5–3   Vacuum Desiccators

to a draft of air is fairly satisfactory for removing residual solvent, especially from large quantities of material. Heating is a good method of drying and may be done on a bath of some type or in an oven. However, there are disadvantages to heating: (1) The wet solid may liquefy below the melting point of the pure compound, especially if the temperature coefficient of solubility is high, (2) the solid may decompose, (3) the solid may undergo oxidation, (4) the solid may evaporate. The complete removal of the solvent may be assured by drying to constant weight.

Small amounts of solvent may be removed by the use of a vacuum desiccator. The factors here are: (1) vapor pressure of the solvent; (2) large surface area of the wet solid; (3) large surface area of the absorbent; (4) low pressure in the system; (5) wide path and short distance between solid and absorbent. Vacuum desiccators for use at room temperature are shown as A and B, Figure 5–3. Type B is very

liable to break.   In the Abderhalden drying pistol C, the solid is dried *in vacuo* while being heated by the vapor of a boiling liquid.

An organic liquid may be absorbed in a nonvolatile liquid or solid with which it is miscible but which does not react to give volatile products, as for example lubricating oil, paraffin, or butyl phthalate.   Water may be absorbed by the drying agents of Chapter 12.

When dry, the melting point of the solid should be determined.   This can be compared with the known melting point, in case the compound is known.   If the identity of the compound is not known, the crystallization process should be repeated, preferably using another suitable solvent, and the melting point taken again.   If there is no change, the compound generally can be considered to be pure.

SECTION 5.5   FILTER PAPER

5.51   Grades and Brands of Filter Paper.   The proper selection of filter paper depends largely on the nature of the material to be filtered and in part on the manner of filtration, as, for example, with or without suction.   When finely divided material, as for example decolorizing carbon (Nuchar, Norite), is to be removed, the paper should be reasonably retentive, whereas, if the material is very finely divided, as for example precipitated barium sulfate, the paper must possess a high degree of retentiveness.   If the material is not finely divided, a coarse-grained paper can be used.   This is usually the case when crystalline solids are being separated from the solution out of which they have been crystallized.   When filtration is done under pressure or under suction, the paper should be more retentive than under normal conditions.   Acid-washed papers are not necessary.   Such papers seldom are used in beginning organic chemistry because of their expense.   Papers not acid-washed often are designated as Qualitative Filter Papers.   In Table 5–2 the

TABLE 5–2

CHARACTERISTICS OF WHATMAN QUALITATIVE FILTER PAPERS

No.
1   Medium weight, speed, and retentiveness; general purpose.
2   Thicker, slower, more retentive than No. 1.
3   Very thick, strong, retentive; medium speed.
4   Softer, more open, faster than No. 1.
5   Hard, tough, close texture, slow, very retentive.
7   Rough surface, medium speed and retentiveness.
12   Fluted, much like No. 1.
50   Hardened, very tough and very close texture; more retentive than No. 5.

properties of Whatman qualitative filter papers are shown. In Table 5–3 are listed other brands so as to indicate their approximate equivalence to the Whatman papers.

TABLE 5–3

COMPARISON OF DIFFERENT BRANDS OF QUALITATIVE FILTER PAPERS

Whatman *	E and D †	Munktells ‡	S and S §
1	613		595
2		1F	
3		100	598
4	615	2	604
5			602
7	617 ‖		597
12			588
50			575

* English.
† Eaton and Dikeman, American.
‡ Swedish.
§ Carl Schleicher and Schuell, now American, formerly German.
‖ Thicker, more open and faster than 615.

Removal of finely divided decolorizing carbon can be accomplished with most of the papers listed in Table 5–3, even from organic solvents, a separation usually more difficult than from water. Even the coarser papers, which allow the finest material to pass at first, later retain it because of clogging (W No. 4, E and D No. 615 and No. 617, S and S No. 588, No. 597, and No. 604). The flow slackens as the paper becomes clogged with fine material. A thick paper such as E and D 617 or S and S 598 maintains its rate of flow better than a thinner paper.

5.52 Folding a Fluted Filter. Select a circular piece of filter paper having a diameter of about 1½ to 2 times that of the funnel and not so large that paper extends above the edge of the funnel after it is folded. First, fold the paper in half (Figure 5–4A). Next, fold in half again as for ordinary filtration, but from here on proceed differently. Open out the last crease so as to have a half-circle; then fold each edge toward the center, making three creases in the same direction. This divides the paper into 4 equal sections, B. Then divide each section by a crease, still in the same direction. This gives 8 equal sections, C. Divide each section in two by a crease in the *opposite* direction, thus making 16 sections, D, and 32 sections when the filter paper is opened, E. When placed in the funnel, the paper forms a fluted cone which consists almost entirely of active filtering surface. Care should be taken to crease the paper strongly at the broad end of the cone but only gently at the apex.

If the apex section is strongly creased, the paper is weakened and may burst from the pressure of liquid above when in use. The apex of the cone *should extend well into the stem of the funnel* so that none of the paper stretches across; otherwise, it may be ruptured, owing to the weight of liquid above.
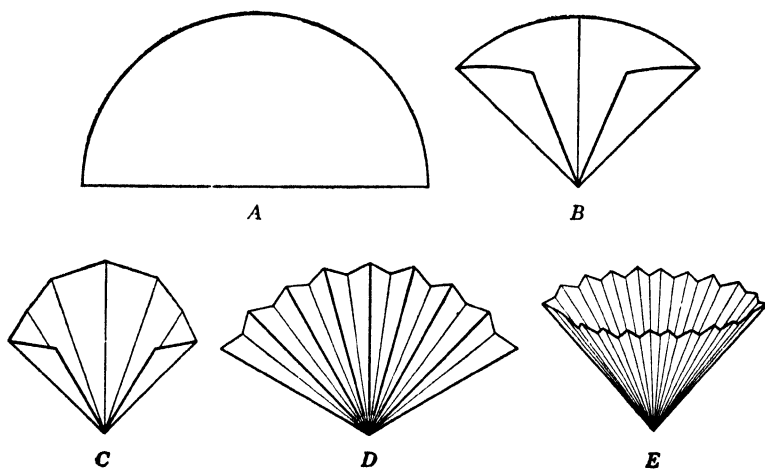
FIG. 5–4   Folding a Fluted Filter Paper

Experiment 5–1   Purification by Crystallization (Note 1)

In a 100- or 200-ml. conical flask provided with a reflux condenser (Notes 2 and 3), place 10 g. of the specially prepared sample of naphthalene (Note 4) and 30 ml. of ethyl alcohol (Note 5). Before heating the contents, assemble the apparatus for filtering the hot solution, consisting of beaker, stemless funnel, fluted filter paper, watch glass, and heater (*A*, Figure 5–1). Add 10 to 15 ml. of alcohol and heat until the funnel is hot (Note 6). Heat the conical flask with a *small* flame, and boil the contents gently for 1 or 2 minutes or until the naphthalene has dissolved.

After the filtering apparatus is hot throughout, pour the hot mixture into the funnel, and cover at once with the watch glass. The filtrate although colored should be clear. If it is not, pour it through the filter until it is clear, keeping it hot. Let stand covered until crystallization is complete, agitating at intervals. Cooling to *ca.* 5° causes more solid to separate. Stir for 1 or 2 minutes before filtering, and take the temperature of the mixture.

Collect the solid on a Buechner or Hirsch funnel of *proper* size. Wash with small amounts of solvent. The solid should be colorless. After all residual solvent is removed, determine the weight. Calculate the percentage recovery in two ways: (1) on the basis of the theoretical amount recoverable from the volume of alcohol used, and (2) on the basis of the initial material taken.

Obtain from the instructor a sample of impure material for purification by crystallization. Carry out preliminary tests with different solvents so as to find one which serves for purifying the main component, as alcohol does for purifying naphthalene. Recall Experiment 2–1, but in this case, owing to the limited amount of solid, add the solvent drop by drop to a small amount of the solid. If there is ready solubility, try another solvent. When a solvent does not readily dissolve the main component in the cold, apply heat. Finally when a satisfactory solvent is found, decide how much to take (refer to 5.22).

Purify by the general procedure already followed in the case of naphthalene, after saving out a small amount for a melting-point determination. After the purified product is entirely free of solvent, take the melting point, determine the weight, and calculate the per cent recovery (Note 7). If the compound is not pure, recrystallize it. Compare the melting points of the crude and purified material. Report to the instructor after completing the write-up.

Notes

1. The directions of this experiment are purposely meager. The student should be familiar with the discussion and should be able to purify naphthalene satisfactorily without the necessity of repeating the experiment.

2. The condenser may be dispensed with but only if the heating is done with a very small flame so that little or no alcohol vapor leaves the flask. The flask should be covered, as with a watch glass. Alcohol vapor will ignite as soon as it comes in contact with a flame.

3. Refer to Experiment 3–1 for comments regarding the drilling of cork stoppers.

4. This consists mainly of naphthalene with which is mixed about 2 per cent of impurity consisting of carbon and methyl orange.

5. The solubility of naphthalene per 100 g. of alcohol is as follows: 5 g. at 0°; 7 g. at 10°; 9.8 g. at 20°; 13.4 g. at 30°; 19.5 g. at 40°; 35 g. at 50°; 67 g. at 60°; 179 g. at 70°.

6. A hot plate is much safer than a flame in cases where flammable vapors may accumulate.

7. The object of the experiment is purification. This always entails considerable loss. However, the amount lost should not, in general, exceed 50%.

Questions

1. At what temperature, if the naphthalene is assumed to be pure, would the solution be saturated?

2. Why is it desirable to minimize evaporation?

3. Why is it desirable to stir the mixture of liquid and solid for 1 or 2 minutes?

4. Why not apply strong suction while the mixture of liquid and solid is being transferred to the filter?

5. Why break the suction before turning off the aspirator?

6. What weight of naphthalene is lost in the filtrate, under the conditions of your experiment?

7. How do you account for the fact that the yield of naphthalene is not quantitative, even after making allowance for that lost in the filtrate?

8. What evidence do you have for believing that the purified sample of unknown material is pure?

Chapter 6

EXTRACTION

Extraction is the removal of a substance from a solid or from a liquid by means of a solvent. The extracting solvent should preferentially extract the required substance without extracting other materials. Extraction is much employed in the separation of substances from reaction mixtures or from natural sources and is useful in the purification of substances.

SECTION 6.1 EXTRACTION FROM A LIQUID

When the substance to be extracted is in solution, as for example in a more or less complex reaction mixture, often it can be extracted by a solvent which is not completely miscible with the original solution, and in which the substance is soluble. The extracting solvent at most should be but slightly miscible with the original solution, and its solvent power for the substance should be greater than that of the original solvent.

6.11 Distribution between Inert Solvents. A substance that is soluble in each of two liquids which are immiscible with each other, dissolves partially in each of them when both liquids are present; that is, the substance is distributed between the two liquids. The concentrations of a substance in the two liquid phases at equilibrium usually are roughly in the ratio of the solubilities of the substance in the two solvents. This ratio of the concentrations of the solute is expressed by the distribution constant K_D:

$$K_D = C_B/C_A \tag{6-1}$$

Here C_A and C_B are the respective concentrations of the solute in solvents A and B. The value of K_D of a solute between two solvents is a constant if both solutions are dilute and if the molecular weight of the solute is the same in both solvents. The concentration of the substance in one phase is always proportional to the concentration of the same specie of the substance in the other phase.

Deviations in K_D with concentration occur if the concentration in either solvent becomes large, or if the solute is associated in one of the phases. As the concentration in either phase becomes large, K_D will vary, even though both solutions are perfect. The reason is that the

dissolved substance changes the nature of the solution. If the solute exists as a monomer in one solvent, and as a dimer in the other, the value of K_D, calculated from the total concentration in each solvent, according to Equation 6–1, varies with the concentration.

A value of K_D calculated from the solubility of the solute in each of the two solvents is valid only if the solubility of the solute is very low in both solvents and if the solvents are completely immiscible.

Oftentimes the two solvents are partially soluble in each other. This is true of a commonly used pair, water–ether (ethyl ether). In such cases the actual distribution constant differs from the one calculated from solubility data, since the solubility of the solute is altered by the presence of the other solvent.

The way many substances are distributed between a typical nonpolar solvent, for example n-hexane, and a typical polar solvent, water, can be predicted from the discussion of Section 2.2, Structural Factors in Solubility. The data of Table 6–1 show in a general way the approxi-

TABLE 6–1

APPROXIMATE DISTRIBUTION CONSTANTS BETWEEN HEXANE, A, AND WATER, B

Substance	$K_D = C_B/C_A$
Water-soluble inorganic acid	Very large
Water-soluble inorganic base	Very large
Water-soluble inorganic salt	Very large
Water-soluble organic salt	Very large to large
Oxygen-containing * or nitrogen-containing † compound	
Low molecular weight	Large to small
High molecular weight	Small
Nonpolar liquid	$<10^{-4}$

* Alcohol, acid, ester, aldehyde, ketone.
† Amine, amide.

mate magnitude of the distribution constants of several types of compounds between these extreme types of solvents. Approximate distribution constants when a solvent has intermediate polarity, as for example ethyl ether, can be estimated from the discussion of Chapter 2.

6.12 Salting Out. Usually the solubility of an organic compound in water is decreased by the presence of a soluble inorganic salt. A water-soluble organic compound may be extracted with an organic solvent more easily from a salt solution than from pure water since K_D (Table 6–1) then is smaller. When extracting an organic substance which is very soluble in water from an organic liquid somewhat soluble in water, such as extracting ethyl alcohol from ethyl ether, an aqueous salt solution

is preferred over pure water, in order to minimize loss of the organic liquid.

6.13 Reaction Solvents. Sometimes separation can be accomplished by means of a reaction solvent, the action of which is discussed in 2.12. Here the material to be extracted is converted into a substance having a different distribution constant. Thus an organic acid or an organic base usually can be converted to a salt which is water-soluble and thus one which favors water in the distribution. Completeness of extraction may be demonstrated by testing the organic phase with litmus paper moistened with water. A complication may arise if the acid or base is very weak, since hydrolysis of the salt may leave an appreciable fraction of the original compound uncombined, which favors the organic solvent. Moreover, it is more difficult to demonstrate completeness of extraction.

6.14 Efficiency of Extraction. The efficiency of an extraction operation depends in part on the distribution ratio and in part on the relative volumes of the two phases. This is shown by Equation 6–2, where f, the fraction of solute remaining unextracted in solvent A after it has been extracted once with solvent B, is expressed in terms of C_i, the initial concentration of the solute in solvent A; C_A, the final concentration of the solute in solvent A; C_B, the final concentration of the solute in solvent B; and v_a and v_b, the respective volumes of solvent A and solvent B.

$$v_a C_i = v_a C_A + v_b C_B$$

$$v_a C_i / C_A = v_a + (v_b C_B / C_A)$$

$$f = C_A / C_i = v_a / (v_a + v_b K_D) \qquad (6\text{--}2)$$

Thus the fraction remaining in the original solvent is expressed in terms of the volumes of the two solvents and of the distribution constant. If the solubility of the solute in the extracting solvent B is three times its solubility in A, the fraction remaining in A is 0.25, when the volumes are equal.

6.15 Repeated Extractions from a Liquid. Usually extractions are carried out a number of times, since one extraction does not remove the solute completely. If the same volume of extracting solvent is used each time, the fraction remaining in solvent A is given by Equation 6–3 where N is the number of extractions:

$$f = C_{A_N} / C_i = [v_a / (v_a + v_b K_D)]^N \qquad (6\text{--}3)$$

Calculation by means of Equation 6–3 shows that, if solvent A is shaken with an equal volume of solvent B divided into four equal parts, the fraction of solute remaining after four extractions is 0.106, whereas 0.25 remains if the solvent is used all at once, assuming $K_D = 3$. This

shows the advantage of several extractions over a single extraction and of dividing a given volume of extracting solvent into several portions. The advantage gained by dividing the extracting solvent is still greater when the value of the constant exceeds 3.

6.16   Emulsions.   Extraction by an immiscible solvent often is rendered troublesome by the emulsification of the two liquid phases. This may result from one or more of the following: (1) the presence of fine particles of solid insoluble in both phases, (2) the presence of a solute which lowers the surface tension between the two phases, (3) the similarity in density of the two phases, (4) vigorous agitation. The emulsion is more troublesome if it results from a combination of two or more causes. In any case centrifuging usually is effective in breaking the emulsion. Often the addition of a small amount of a third substance, especially ethyl ether, will break an emulsion. Sometimes heat is effective.

Fine particles are effective in stabilizing emulsions in that they form protective coatings around the droplets and prevent them from coalescing. This is remedied by filtering the solution before the extracting solvent is added.

When a solute is present which lowers the surface tension of the interface of the solvents, the tendency for the droplets to coalesce is greatly minimized. Often the surface tension can be increased, when one of the solvents is water, by the addition of a salt highly soluble in water. If the solution is basic, the addition of a strong acid usually helps, and if it is acidic, sometimes a little base will help. However, emulsions are more likely to be stabilized under basic conditions, probably because soaps are then present, owing to the presence of organic acids, usually as impurities. In general, therefore, the addition of a strong mineral acid, preferably hydrochloric acid, is useful in breaking emulsions.

Similarity in density lowers the rate with which the two liquid phases separate. The density of either or both phases may be changed by one or more procedures: (1) dilution with more of the pure solvent; (2) addition of a third solvent of widely different density which is miscible with one but not with the other solvent; (3) addition of a solid that is readily soluble in one but not in the other solvent.

Vigorous agitation, although desirable as a means of obtaining good contact between the phases, sometimes may lead to a much worse emulsion than would result if the two liquids were agitated gently but over a much longer period of time. Some solvents form emulsions with aqueous solutions much more easily than do others. Chloroform especially requires careful manipulation.

6.17   Methods of Extraction from a Liquid.   From the standpoint of economy, as small a volume of extracting solvent as possible should be

used when one liquid phase is to be extracted by another, for it is a saving in time, effort, and material. It is desirable that the extracting solvent be favored greatly by the extractible substance, that the contact area between the phases be large and that the maximum power of the solvent be utilized. This last is aided by repeated use of the solvent, as for example by evaporation from the extracted substance and re-use.

In small-scale operations where the extracting solvent is favored by the solute, the usual procedure consists merely in shaking the two liquids in a separatory funnel, removing the solvent, and repeating with one or more portions of the solvent, until the extraction is reasonably complete. When one of the solvents has a high vapor pressure at room temperature, the pressure within the separatory funnel may greatly exceed that of the atmosphere and lead to blowing out of stopper or stopcock. Thus it is necessary to relieve the pressure at frequent intervals. This is done most conveniently by inverting the separatory funnel and then opening the stopcock.

A   B
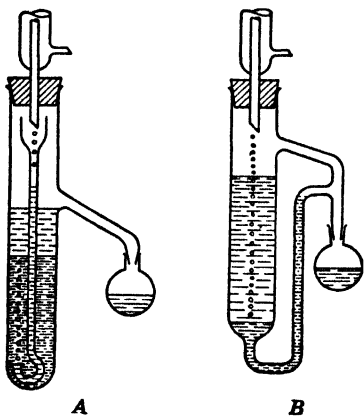
FIG. 6-1 Apparatus for Continuous Extraction of a Liquid

When the lighter phase is water, usually it is convenient to use two separatory funnels, one above the other, so that the heavier organic liquid can be run directly from one funnel into the second. Purification is aided by having the next wash liquid in the second funnel and letting the organic liquid flow, drop by drop, through it. Usually some of the heavier organic phase floats on top of the water. Most of this organic liquid can be made to fall by adding water until the upper surface enters the neck of the separatory funnel.

Continuous extraction usually is necessary when the distribution opposes rather than favors extraction by a given solvent. This is done by boiling the solvent into a reflux condenser (see 7.23 and Figure 7-2, Condensers), allowing the condensate to flow into and through the liquid containing the solute being extracted, and returning the solvent to the boiler, from which it repeats the extraction cycle. In this way, the solute is extracted by a much smaller volume of solvent than is possible by repeated extractions in the usual way.

Types of apparatus for continuous extraction are shown in Figure 6-1, A and B, where the extracting solvent is lighter and heavier, respectively, than the solution. The efficiency of the process depends on hav-

ing the extracting liquid dissolve the amount of solute that would bring
the phases into equilibrium. The time of contact may be lengthened
by making the extractor tube long, or by slowing the rate of passage of
the extracting liquid by baffle plates or by spiral tubes. The interface
area may be increased by dividing the extracting medium into fine drops,
as for example by passing it through a fine orifice or through a sintered
glass plate.

<div align="center">A   B   C   D</div>
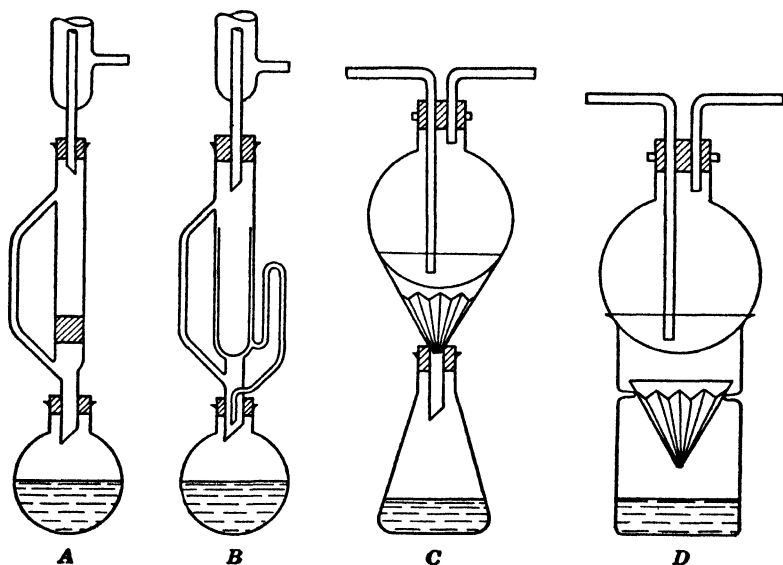
<div align="center">Fig. 6–2   Apparatus for Continuous Extraction of a Solid</div>

SECTION 6.2   EXTRACTION FROM A SOLID

Repeated extraction from a solid mixture may be employed if the solid
desired is readily soluble in the extracting solvent. It is accomplished
by shaking the mixture with the extracting solvent and separating the
two phases by decanting, filtering, or centrifuging. Sometimes a system
containing a solid is converted to a liquid system by the addition of
another suitable solvent.

Continuous extraction is necessary when the solid is only slightly
soluble in the extracting solvent and often is employed even when the
solid is soluble, because of the convenience. The principle is similar to
continuous extraction of a liquid.

In Figure 6–2 are shown different types of apparatus for continuous
extraction of a solid. In A the solid is supported in a vertical tube on a
sintered glass plate fused into the tube. In the Soxhlet type B the solid

is contained in a thimble of filter paper. This gradually becomes full of the liquid, which automatically siphons out from time to time.

Satisfactory apparatus for continuous extraction from a solid can be assembled from laboratory glassware usually available, in case the more complicated pieces, *A* and *B* (Figure 6–2) are not available. These are shown as *C* and *D*. Here the condenser is a round-bottomed flask through which cold water circulates. This sets on top of a funnel in *C* or on top of a beaker without pour out in *D*. In *C* the stem of the funnel must be wide, and the paper (or the funnel) must be fluted, to permit upward passage of the vapor. In *D* the funnel is supported by four indentations in the side of the beaker. This last has the advantage that the solid is kept hot by the vapor of the solvent. The extraction proceeds more rapidly on this account.

Experiment 6–1   Distribution between Immiscible Solvents

In this experiment the organic dibasic acid, succinic acid $HOCOCH_2$-CH_2COOH (molecular weight, 118.1) is distributed between two liquids, ethyl ether $(C_2H_5)_2O$ (b.p. 34.5°, *Caution:* Note 1) and water. From the results obtained the student will be able to judge in which of the two solvents the acid is the more soluble. Also he should be able to decide if the ratio of solubilities is a constant over a range of concentrations.

In a clean 250-ml. Squibb separatory funnel with well-fitting stopper and stopcock (Note 2) place 60 to 75 ml. of a solution of succinic acid in ether (approximately 0.1 *M;* see instructor). Determine the concentration of acid in the ether solution by titrating 10 ml. with 0.05 *N* sodium hydroxide, using phenolphthalein as indicator (Notes 3 and 4). Add about 10 ml. of distilled water, agitate for a moment or so by a rotatory motion before inserting the stopper, then quickly invert, and open the stopcock to release the pressure. Shake once or twice, and then release the pressure as before. Continue until the pressure increase on shaking is negligible. Then shake the contents *vigorously* for 1 or 2 minutes, or until you believe that equilibrium is established. Support the separatory funnel in a ring and, after the two layers have separated so that each is clear, draw off the water phase into a small beaker. Determine the concentration of acid in each phase by titrating a definite volume, 10 ml. of the ether, and 5 ml. of the water phase, with 0.05 *N* sodium hydroxide, using phenolphthalein as indicator.

Add more water, 8 or 10 ml., to the ether remaining in the separatory funnel, and shake as before. Determine the concentrations as previously. Repeat, but with 12 ml. of water instead of 10 ml., so that larger samples may be taken for the third analysis.

From the results, calculate the concentrations of succinic acid expressed as moles per liter, in the two solvents. Calculate also the value of the distribution constant at each equilibrium stage (Note 5).

Calculate the fraction of succinic acid that would have remained in the ether phase after three extractions with 10 ml. of water each time, assuming that no ether has been removed.

Notes

1. Because ether vapor is inflammable, care must be exercised to keep it away from flames. Owing to the high vapor pressure of the liquid, ether vapor leaves the vessel and, since it is heavier than air, drops onto the desk top. If flames are near, the vapor may inflame or produce an explosion.

2. Test the separatory funnel beforehand for leakage by adding a few milliliters of ether and shaking, as in the experiment. Neither the stopper nor the stopcock should leak.

3. Burettes and pipettes may be obtained from the instructor or from the storeroom. The ether solution should be forced into the pipette by pressure, considerably past the mark. In order to do this, the separatory funnel may be closed with a two-hole rubber stopper, through one hole of which air can be forced by means of a glass bend and a piece of rubber tubing, while through the other hole the stem of the pipette is inserted. Or the rubber stopper may have only one hole, and carry a T tube with the side arm horizontal. The pipette is inserted vertically down the T tube through an air-tight rubber connection. Air pressure is applied at the side arm of the T tube.

4. Beforehand construct a table in the notebook so that the data may be incorporated neatly as soon as obtained. The table should show the volumes of solutions taken for analysis, the burette readings, the strength of alkali solution, the volumes of alkali used, the concentration of succinic acid in moles per liter of solution, and the distribution constant.

5. Variation in the constant is due to a difference in the molecular weight of succinic acid in the two phases. The effect of ionization is minor.

Questions

1. What are the relative densities of ether vapor and air?

2. Why does the pressure increase at first between successive shakings of the mixture of water and ethyl ether? Why does it not increase after several shakings?

3. Why not draw the ether solution into the pipette by suction?

4. In which solvent is succinic acid the more soluble, water or ether?

5. What would you do in order to remove 95% of the succinic acid from the ether?

6. Taking into account the fact that water is slightly soluble in ether (about 2%), what would you do in order to remove by means of a definite volume of ether, as for example 5 times the volume of the water, 90% of succinic acid from any solution of succinic acid in water?

7. How can the volume molar concentrations you obtain be converted into weight molar concentrations?

8. Show how, from the trend in the values of K_D, you can decide in which solvent the molecular weight is greater.

9. Explain why the effect of ionization is minor.

Chapter 7

DISTILLATION

Distillation is a process whereby a liquid is converted into a vapor and then back to the liquid. The two essential processes are vaporization and condensation. Distillation is extensively employed in the organic laboratory for purposes of purification.

The essential pieces of apparatus assembled for distillation, as shown in Figure 7–1, are: the distilling flask A, thermometer B, condenser D, receiver E, and burner F. Less essential are the adapter G and guard tube H.

SECTION 7.1 VAPORIZATION

7.11 The Boiler. The choice of the distilling flask A is governed by two factors, the volume of the liquid to be distilled and the temperature of distillation. The flask must not be so small that it is filled more than two-thirds full, since otherwise by the time the temperature of the liquid reaches that of the boiling point the accompanying expansion may cause the liquid to fill the flask completely. Also the agitation during boiling may be sufficient to splash liquid through the side arm.

The flask should not be too large for then an appreciable quantity of liquid may be left behind even if the distillation has been carried to dryness. The amount of vapor left behind in a flask, especially in the case of a high-molecular-weight substance, may amount to several grams.

The position of the side arm C on the distilling flask is governed by the boiling temperature. If the boiling temperature is high, the side arm should be as low on the neck as possible, in order that very strong heating will not be necessary to drive the vapor over. Insulation of the flask below the neck also decreases heat loss and increases rate of distillation. If decomposition occurs at the boiling temperature, vacuum distillation or steam distillation should be resorted to, as discussed in Chapters 8 and 10. The side arm C of the distilling flask should slope upward from the neck before bending down toward the condenser (Figure 7–1) in order to prevent liquid which condenses around the stopper from flowing down into the condenser. By this arrangement, only vapor passes into the condenser.

The thermometer *B* should extend into the neck so that the entire bulb is below the side-arm opening and well submerged in the vapor stream. Only when the bulb is wet with liquid is it reasonably certain that the temperature recorded is the equilibrium temperature between liquid and vapor. However, even then the temperature may read high, owing to superheating of the liquid on the bulb.
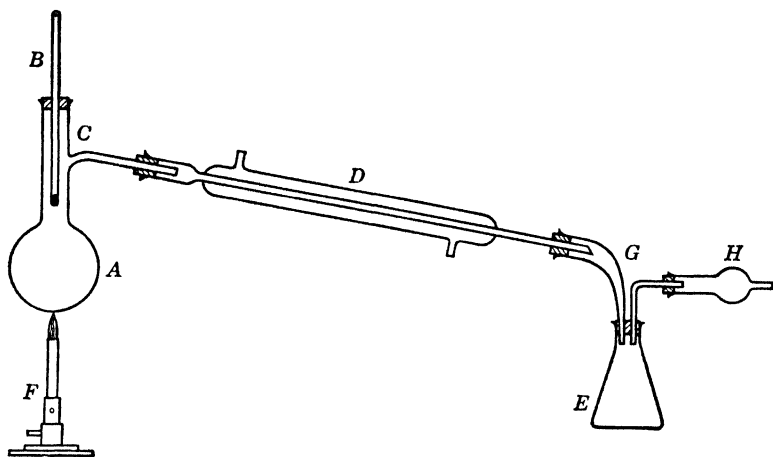
FIG. 7-1   Typical Setup for Distillation

7.12   Heating. Heat may be obtained from three sources: flame, electricity, or steam. Usually a gas burner *F* is employed either with or without a wire gauze or liquid bath under the flask. The flame should be close to the flask for good control, should not be any larger than necessary, and especially should not extend above the surface of the liquid, since this may cause decomposition of the compound or fracture of the flask. It certainly causes superheating of the vapor. A direct flame has a disadvantage toward the end of the distillation, for decomposition may take place, owing to the fact that the glass may be excessively overheated when an attempt is made to distil the last portions of liquid.

Electric heat may be supplied from a hot plate, an internal heater, or a radiant heater. The hot plate has the advantage over the flame that it is safer to use with flammable liquids since it will not ignite most of them in case of an accident. However, it will ignite carbon disulfide and sometimes ether if the plate is hot enough or if hot wires are exposed. The hot plate has some disadvantages: (1) high heat capacity, (2) few fixed heats, (3) poor contact with a distilling flask. The internal heater has the advantage of being more efficient, but it has the disadvantage

of bringing hot metal in contact with the liquid. The radiant heater has the advantage of being built in a convenient form and able to supply radiant heat to the liquid, thus avoiding excessive heating of the flask wall. This is especially useful when one is trying to distil over a last portion. Electric mantles have similar advantages.

Heating by means of a liquid bath is indicated whenever it is desirable to distribute the heat as uniformly as possible over the surface of the vessel being heated, especially for overcoming bumping due to solids (see 7.15) or inherent in vacuum distillation (Chapter 8). The bath can be heated by either gas or electricity. A large surface of contact with the flask is possible, and various temperature gradients are available between the flask and bath. This allows the rate of distillation to be varied over a wide range. Except where the desired temperature is the boiling temperature of the bath liquid, *a thermometer should be suspended in the bath*. A bath is almost essential where a large amount of solid is present in the flask, in order to cut down bumping. It is useful also in driving over a last portion since this is not so likely to be decomposed as when heating is done with a flame.

Water is the best bath liquid when distilling a liquid boiling up to *ca.* 75°. It is especially useful at its boiling temperature, as then the temperature remains constant at 100°. Constant-level water baths are particularly convenient since they are automatic and are not subject to the marked temperature fluctuations associated with manual additions of cold water.

A wax or paraffin bath, because it is solid at room temperature, has the advantage over a substance that is liquid at room temperature, inasmuch as the contents cannot spill when cold. However, the flask should be removed before the liquid solidifies; otherwise, difficulty is

TABLE 7-1

MEDIA FOR HEATING BATHS

	M.P., °C.	Useful Range, °C.
Water	0	To 100
Cottonseed oil		To 200
Glycerine		To 200
Butyl phthalate		To 250
Sulfuric acid *		To 275
Paraffin (ceresin)	50	50–175
Hydrogenated cottonseed oil †	60	60–250
Potassium bisulfate	210	210–400

* May be decolorized by 1 drop of HNO_3.
† More stable than cottonseed oil.

sometimes encountered in cleaning the outside of the flask. Sometimes a solid such as sand is used as a bath to prevent the direct heating of the glass. Some substances that are useful in baths are listed in Table 7–1.

Steam also may be used as a heating medium. A steam funnel is a useful device for playing steam on the bottom of a flask. Steam is especially valuable in distilling very inflammable liquids since it may be generated at some distance from the distillation and no flame is necessary in the immediate vicinity.

7.13 Phenomenon of Boiling. Constant evaporation takes place from a liquid surface except when the space above it is saturated with vapor, that is, when the liquid and vapor are in equilibrium. Normally liquids in open vessels are at a lower temperature than the surroundings, owing to the fact that heat is being removed as the liquid evaporates. When heat is supplied to the liquid, part of it is used to evaporate the liquid. When the amount of heat supplied exceeds the amount utilized by the evaporation process, the temperature of the liquid rises. When the temperature of a liquid reaches the point where its vapor pressure is slightly above the pressure that is applied to the surface of the liquid, vapor formation can take place in the body of the liquid. The resulting disturbance is termed boiling. Even though the space above the boiling liquid is saturated by vapor, vaporization continues since vapor actually is forced out of the liquid into the space above, because the vapor pressure of the liquid exceeds the applied pressure. The temperature at which the vapor pressure is just equal to the applied pressure is the boiling temperature. The boiling temperature at 1 atmosphere pressure is called the **boiling point.**

The boiling temperature is a constant at a given pressure under conditions that permit smooth boiling. Under such conditions this temperature does not change with the vigor of boiling except in a minor way, as the degree of superheating changes. Since the liquid's vapor pressure is actually above the applied pressure at the surface, the liquid must be superheated before boiling can take place.

Superheating is necessary before boiling can take place at atmospheric pressure, as for example in an open vessel, because the vapor pressure of the liquid must exceed atmospheric pressure by a pressure equal to the weight of the liquid above the point of bubble formation. In addition, another and much more important pressure which must be overcome is the surface tension of the liquid. The tendency of a bubble to collapse, resulting from the surface tension of the liquid, must be balanced by the pressure within the bubble. Equation 7–1 gives in milli-

meters of mercury the pressure p inside a bubble in terms of the radius r in centimeters, and the surface tension γ in dynes per centimeter.

$$p = 15 \times 10^{-4} \, \gamma/r \qquad\qquad (7\text{--}1)$$

The smaller the bubble, the greater must be the pressure within the bubble to prevent collapse. At zero radius, this pressure becomes infinite. Conversely, the vapor pressure would have to be infinite in order for a bubble to start from zero radius. Actually, however, there usually are flaws in the glass and particles of dust or bubbles of air in the liquid. These serve as nuclei of finite radius in which the bubble may start. Nevertheless, under ordinary conditions of boiling, the temperature of the liquid is usually a few degrees above the boiling point. If a liquid is carefully freed of air by boiling and then cooling, it is possible to raise the temperature considerably above the boiling point. Water has been raised to 137°C. before it boiled. Of course, once the bubble forms, it rapidly increases in size because of the large vapor pressure of the liquid. Often in the case of superheating, the bubble expansion takes place with explosive violence, sometimes throwing the liquid out of the container and possibly shattering the container. This is called bumping.

7.14 Bumping Remedies. *In no case should a liquid be boiled without the addition of a boiling aid.* Bumping is stopped by adding to the liquid a source of bubble nuclei, such as a boiling chip, a platinum wire, or an ebullition tube. Boiling chips are most commonly used. They are small chips of clean hard porous plate or tile about 2 to 5 mm. in diameter. The small pores induce even boiling. Usually only two or three small chips are necessary. They have the disadvantage of disintegrating slightly and contaminating the residue. Also they can be used only once since the air is removed by boiling. Nevertheless, vapor continues to occupy pores during continued boiling. However, if the liquid drops below the boiling temperature at any time, vapor condenses, and liquid enters the pores. Then it usually is necessary to add other chips. Platinum wire acts as a porous material supposedly because of dissolved gas. It has the advantages that it still offers protection when the liquid is heated after cooling from a previous boiling, and also it is removed readily from the residue.

An **ebullition tube** is one of the best devices to aid boiling. It can be made easily, it does not contaminate the liquid, and it can be used repeatedly. This is a glass tube about 3 mm. in diameter, sealed about 5 mm. from the bottom, so that there is an open cup about 5 mm. long. The tube should be long enough to reach well into the neck of the vessel so that it remains vertical. A crook at the top facilitates removal. When placed in the liquid, the cup on the bottom remains full of air and

serves as a chamber into which the liquid may vaporize. In the course of the boiling, the air is removed and replaced by vapor. However, since the liquid is still slightly superheated, the chamber remains full of vapor. But on any cooling the chamber fills immediately with liquid, and the ebullition tube no longer offers any protection. However, it may be reconditioned by shaking out the droplet of liquid. *If a liquid begins to bump, it must be allowed to cool somewhat before the boiling aid is added,* for, if the liquid is superheated, the intensified boiling that ensues may proceed with explosive violence.

7.15 Bumping Due to Solids in Bottom of Container. A layer of solid along the bottom of the container may be the cause of violent explosive bumping. When the heating of such a mixture is localized, the liquid may be driven away from a small section of the bottom and kept away by a dam of the solid. The heated portion becomes quite hot, and, when the liquid seeps through the solid, two things may happen. Either the rapid vaporization of the liquid when it meets the hot zone causes a vigorous bump or the hot glass cracks when the cooler liquid touches it. If either occurs, a dangerous explosion may result. Sometimes a student, by adding many boiling chips to the liquid, forms a layer on the bottom of the flask, and unwittingly creates a worse hazard than the one he aims to avoid. Bumping may be minimized by supplying heat through a small temperature gradient and over a large surface, as for example by the use of a liquid bath in which a flask is immersed, or by means of an electric heater of the radiant type.

<center>SECTION 7.2   CONDENSATION</center>

7.21 The Condenser. The condenser D (Figure 7–1) is the apparatus for removing heat from the vapor and thus causing it to return to the liquid state. The most common laboratory condenser is the Liebig condenser A (Figure 7–2), a long glass tube into which the vapor passes and which is surrounded by an outer glass jacket through which water may be circulated. A serious drawback is that the condensing tube is glass and thus is a very poor heat conductor. For complete condensation a certain minimum amount of heat must be removed. Moreover, the distillate should be cooled to a temperature where the vapor pressure is low. Therefore a sufficient temperature gradient and enough contact with cooling surface must be maintained to permit sufficient heat transfer. This may be aided by using a long condenser and setting it at an angle with the vertical, to induce convection currents.

For low-boiling liquids such as ether, the condenser should be long, *ca.* 90 cm., and cooled by ice water if possible. For high-boiling liquids,

a shorter condenser may be used. For liquids boiling above 150°, the water jacket is dispensed with and merely the inner tube is used as an **air condenser.** If the outer jacket is not removed, difficulties may

Liebig *	West *	West †	Spiral ‡	Allihn *
A	B	C	D	E

Friedrichs †	Inside coil †	Cold finger §	Dewar type for liquid bath §
F	G	H	I
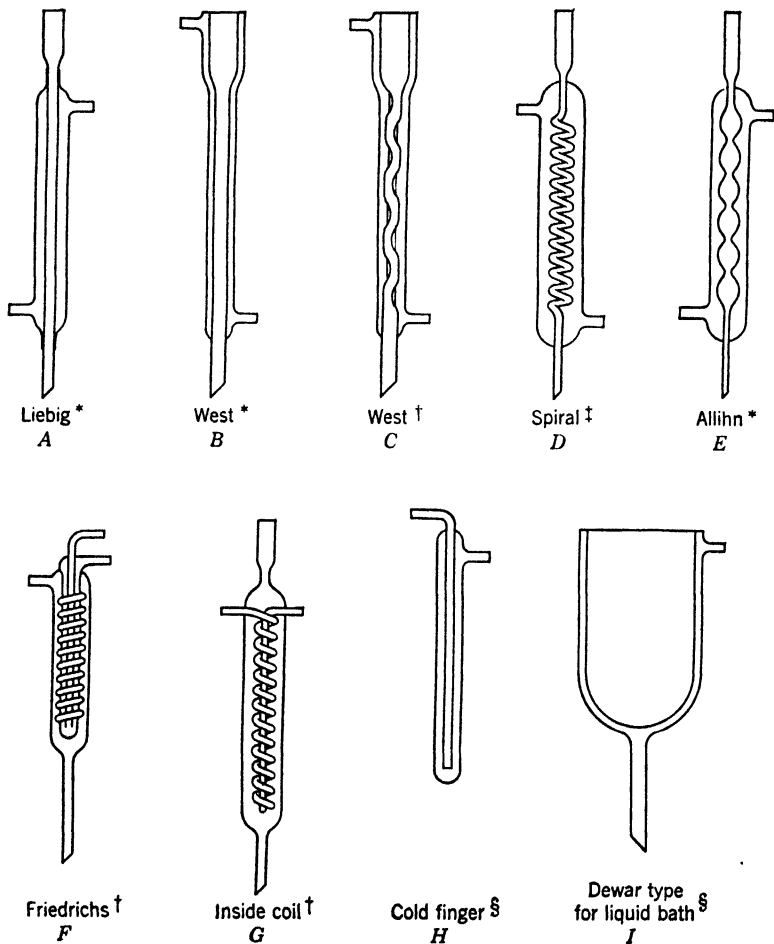
* For distillation or refluxing, preferably slanted
† For distillation or refluxing, preferably vertical
‡ For distillation, vertical
§ For refluxing, vertical

FIG. 7-2   Condensers

arise in that: (1) The empty jacket acts as an insulator; and (2) the rubber connections may melt. When the distillate is a solid at room temperature, the side arm of the distilling flask and the condenser must be large enough so that they will not be clogged by the solid and so that

the solid can be easily removed. The condenser may be kept above the melting point of the distillate by direct heating of the condenser tube with a flame or by an electrically heated resistance-wire wrapping.

For a very high-boiling liquid, especially one boiling above 250°, the side arm of the distilling flask can serve as an air condenser.

A condenser should be used efficiently. A long one should not be selected unless necessary, since it is less convenient than a short one and has a greater holdup. If the vapor seems to be condensed immediately on entering the condenser, full use is not being made of the condenser, and the distillation rate may be increased as long as the distillate comes out of the condenser cold. Actually, nearly all the heat that is put into the flask must be removed in the condenser at the same rate as it goes in. Since heats of vaporization differ for different liquids, different amounts of liquid are evaporated by the same amount of heat, and different amounts of vapor are condensed by the same amount of cooling. A good example is the comparison of toluene (b.p. 110°) and water (b.p. 100°). Water has a heat of vaporization of 540 cal. per gram, whereas toluene has a heat of vaporization of 86.5 cal. per gram. A condenser that can just handle 10 g. of toluene per minute cannot handle even 2 g. of water per minute.

Other types are available besides the Liebig condenser. The West condenser B and C (Figure 7–2) is similar to the Liebig but is in one piece and has a narrower water jacket and thus a greater velocity of flow of cooling water along the outer wall of the inner tube. In other condensers the area of the cooling surface is increased by changes in shape, as for example by alternate increases and decreases in diameter E, by bumps and depressions C, or by being wound in a spiral D, F, and G. In others the cooling medium is surrounded by vapor space as in the Friedrichs condenser F.

7.22 The Receiver. The receiver E (Figure 7–1) preferably is a flask rather than a beaker because: (1) The loss by volatilization is less; (2) the fire hazard is less; (3) contamination by dust and by moisture is less. The attachment of the flask to the condenser by means of the adapter G is desirable if the liquid being distilled is very volatile, or if it is decomposed when in contact with the air of the room, or if it is a disagreeable substance, for example a lachrymator. Ordinarily, however, the distillate may be collected directly in the flask.

The tube H is attached when either the flask contents need protection from the air of the laboratory or the laboratory needs protection from the distillate. Thus, when the flask must be cooled, because the distillate is very volatile, a calcium chloride tube is needed to prevent moisture from condensing on the distillate. When a corrosive liquid such as

acetyl chloride is being distilled, a soda lime tube is needed, to prevent vapors of acetyl chloride from escaping.

A long rubber exhaust tube should be attached to E (or to H) whenever the distillate is a very volatile easily inflammable liquid, for example ether or carbon disulfide. The open end of the tube should be placed outside a window, or near the floor of the laboratory, so that the vapor will not flow along a desk top and come in contact with a flame.

7.23   Refluxing. Often it is necessary to heat a mixture at its boiling point for some time. This is easily done by condensing the vapor and returning it to the boiler. This is called **refluxing.** The principles used in refluxing are those of distillation. However, provision must be made for the counterflow of liquid and vapor through the bottom of the condenser. The opening should be wide and beveled, for this facilitates the return of the liquid from the bottom tip of the inner tube without clogging it, while the vapor passes into the condenser freely. Sometimes small holes blown in the side of the tube are useful in minimizing clogging. The spiral condenser is not satisfactory, since the inner tube usually has a small diameter.

The effectiveness of condensers for refluxing (see Figure 7–2) is in the order, $G > F > E > C > A$ and B, when used in the manner recommended. Slanting of the condenser not only increases the effectiveness in the case of A, B, and E, but also has the advantage that, in case of accident or too vigorous heating, any liquid that spurts out of the condenser is not so liable to fall back onto the fire below. The liquid bath condenser I is especially useful if the cooling medium is ice, or Dry Ice. The cold-finger condenser H is used only for refluxing. It may be inserted into the neck of an open long-necked flask and has one advantage that often it need not be fitted to the flask.

The condenser used in refluxing need not be large, for usually gentle refluxing is sufficient. The temperature accompanying vigorous refluxing is only slightly above that accompanying gentle refluxing. The only advantage of vigorous refluxing is mechanical mixing of heterogeneous systems. Sometimes a guard tube is attached at the exit of a reflux condenser, when it is desirable to protect the liquid from the air.

Chapter 8

VACUUM DISTILLATION

Often substances cannot be purified by simple distillation as described in Chapter 7 since they begin to decompose at temperatures below the boiling point. However, distillation is possible if the pressure in the distilling flask is lowered so that the liquid boils at a temperature below the decomposition point. Such a pressure can be realized for a large number of organic compounds. Distillation at pressures below atmospheric is called distillation *in vacuo* or, more simply, vacuum distillation. Actually the pressure usually is many times greater than the so-called "high vacuum" (less than about 0.001 mm.).

SECTION 8.1 VAPOR PRESSURE

The vapor pressure of a solid or a liquid at a given temperature is the pressure the vapor will exert when it is in equilibrium with the condensed state at that temperature. The liquid–vapor equilibrium is discussed here, but the solid–vapor equilibrium is discussed under Sublimation in Chapter 11.

8.11 Effect of Temperature on the Vapor Pressure of a Pure Liquid. When the temperature of a pure liquid rises, the vapor pressure increases. This follows from the principle of Le Chatelier, since heat is always absorbed in the transition from liquid to vapor. The quantitative relationship between temperature and vapor pressure is given by Equation 8–1 which integrates to give Equations 8–2 and 8–3.

$$d \ln p / dT = \Delta H_v / RT^2 \qquad (8\text{--}1)$$

$$\log_{10} p = -(\Delta H_v / 4.575T) + \text{constant} \qquad (8\text{--}2)$$

$$\log_{10} p_2 / p_1 = \Delta H_v (T_2 - T_1) / 4.575 T_1 T_2 \qquad (8\text{--}3)$$

Here, p_1 and p_2 are the vapor pressures at T_1 and T_2, the respective temperatures on the absolute scale; R is the universal gas constant, 1.99 cal. per mole; ΔH_v is the change in heat content in calories when 1

mole of the liquid is evaporated. It is called the **molal heat of vaporization.** In the integration this latter quantity is assumed to be constant over the range T_1 to T_2. Figure 8–1 shows how the vapor pressure varies with the temperature in the case of benzene.

Figure 8–1B shows how the logarithm of the vapor pressure varies with the reciprocal of the absolute temperature. The straight-line character of the curve is what would be expected from Equation 8–2, if ΔH_v remains constant. By the use of this relationship between the

A
Vapor pressure against
temperature

B
Log. of vapor pressure
against reciprocal of
temperature
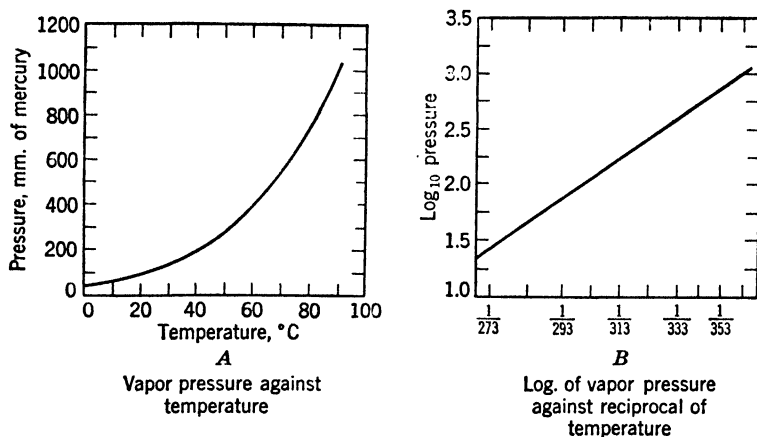
FIG. 8–1   Change of Vapor Pressure of Benzene with Temperature

logarithm of the vapor pressure and the reciprocal of the absolute temperature it is possible to approximate the boiling temperature of any pure substance at any pressure if the boiling temperatures at two pressures are known. The boiling temperature at any pressure may be found by calculation from Equation 8–2 or 8–3, or by the use of Figure 8–2.

In Figure 8–2 the ordinates are pressures on a logarithmic scale, and the abscissas are boiling temperatures plotted on a scale which is linear with respect to the reciprocal of the absolute temperature. It is evident from the several curves that the plots for a given pure substance give reasonably straight lines. Thus, if one knows the vapor pressure of a liquid at two temperatures, the approximate vapor pressure at a third temperature may be obtained by linear extrapolation. It is possible to extrapolate from a single point by using the other curves on the plot as guides, since the curves are roughly parallel. One may use Figure 8–2 to predict approximate boiling points at other pressures. This is the chief usefulness of the figure.
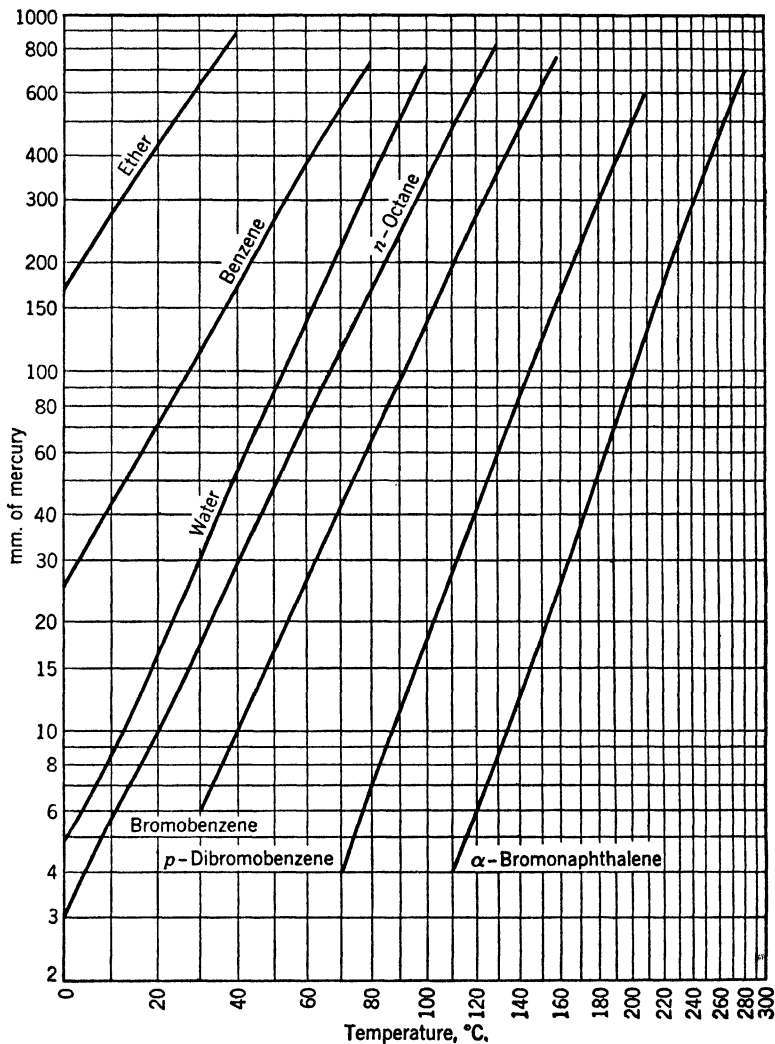
FIG. 8–2   Graph for Approximating Boiling Temperatures
Vapor Pressure (logarithmic scale) against Temperature (scale linear to reciprocal of
absolute temperature)

8.12 Heats of Vaporization. The experimentally determined heats of vaporization at 760 mm. of some common liquids are listed in Table 8–1, in the order of the boiling points of the liquids. It is evident that, in general, the higher the boiling point, the greater the molal heat of vaporization. However, some exceptions are noted, namely, ethyl alcohol, water, and acetic acid.

TABLE 8–1

HEATS OF VAPORIZATION OF SOME COMMON LIQUIDS AT 760 MM.

Liquid	Heat of Vaporization		Boiling Temp., °C.	$\Delta H_v/T_b$
	cal./g.	kcal./mole		
Butane, C_4H_{10}	91.5	5.3	0	19.4
Ethylamine, $C_2H_5NH_2$	146	6.6	15	22.9
Hydrogen cyanide, HCN	210	5.7	20	19.0
Ethyl ether, $(C_2H_5)_2O$	83.9	6.2	34.6	20.6
Ethyl bromide, C_2H_5Br	59.9	6.6	38.4	21.2
Acetone, $(CH_3)_2CO$	124.5	7.2	56.1	21.9
Bromine, Br_2	44.9	7.16	58.8	21.6
Hexane, C_6H_{14}	79.3	6.8	68.7	20.6
Ethyl acetate, $CH_3COOC_2H_5$	88.4	7.7	77.1	22.0
Ethyl alcohol, C_2H_5OH	204	9.4	78.5	26.8
Acetonitrile, CH_3CN	174	7.1	80	20.1
Benzene, C_6H_6	94.3	7.35	80.1	20.8
Water, H_2O	539.6	9.72	100	26.0
Toluene, $C_6H_5CH_3$	86.5	8.0	110.6	20.9
Acetic acid, CH_3COOH	96.8	5.8	118.1	14.8
Butylacetate, $CH_3COOC_4H_9$	73.8	8.5	124	21.4
Chlorobenzene, C_6H_5Cl	77.6	8.8	130.6	21.8
Ethylene bromide, $C_2H_4Br_2$	46.2	8.6	131.5	21.3
Aniline, $C_6H_5NH_2$	103.7	9.5	184.4	20.8
Nitrobenzene, $C_6H_5NO_2$	79.1	9.8	211	20.3
Naphthalene, $C_{10}H_8$	75.5	9.7	218	19.8

8.13   Trouton's Rule.   An approximation to the heat of vaporization at the boiling temperature at 760 mm. is obtained by multiplying the boiling point on the absolute scale by 21 (Trouton's rule, Equation 8–4).

$$\Delta H_v/T_b = 21 \qquad (8\text{–}4)$$

Here ΔH_v is the molal heat of vaporization expressed in calories, and T_b is the boiling point on the absolute scale. In Table 8–1 values of Trouton's constant are given for a number of substances. The value holds well for nonassociating liquids, such as

FIG. 8–3   Change in the Molal Heat of Vaporization of Water with Temperature

ether, pentane, and benzene, but does not hold for substances whose molecular aggregation is different in the liquid and vapor states. It is larger for associating liquids, for example ethyl alcohol and water, and smaller for associating vapors, for example acetic acid.

8.14 Correction of the Boiling Point for Pressure Deviation.
When the pressure deviates slightly from 760 mm., the correction to be
applied for a difference of 10 mm. in pressure may be found by divid-
ing the boiling point on the absolute scale by certain factors. The factor
is 850 if the liquid is normal (nonassociating) and 1020 if associating.
However, such approximations do not hold well if the pressure is
markedly different from atmospheric, mainly because heats of vaporiza-
tion are not constant over a wide range of temperatures, as shown by
Figure 8–3. Here ΔH of vaporization of water is plotted against the
temperature.

SECTION 8.2 PROCEDURE FOR VACUUM DISTILLATION

The types of apparatus used in a vacuum distillation (Figures 8–4
and 8–5) are quite similar to those used in an ordinary distillation except
that various alterations and additions must be made. These deal with
(1) protecting against air leaks, (2) heating and bumping, (3) condensing,
(4) collecting the distillate, (5) evacuating the system, (6) measuring
the pressure, (7) controlling the pressure, and (8) changing the
receiver.

8.21 Protecting Against Leaks. The system usually is put to-
gether with rubber, that is, rubber stoppers and heavy-walled rubber
tubing (so-called pressure tubing). Preferably tubing should have an
inside diameter of not less than 6 mm. The dustlike coating should be
removed from both, especially from the inside of the tubing, by boiling
for a few minutes with dilute acetic acid or sodium hydroxide solution
or better yet by vigorous scrubbing with a cleaning powder, followed by
thorough washing. A very thin coating of glycerol, especially on the
inside of the tubing, facilitates later removal from glass tubes. Rubber
stoppers should enter about half way. If too small, they may be pulled
into the apparatus, and, if too large, they tend to pop out when the
vacuum is broken since they usually swell by absorbing organic vapors.
Duprene stoppers are more resistant than rubber stoppers to organic
solvent action.

If the vapor of the organic compound rapidly attacks rubber, well-
fitted cork stoppers or all-glass apparatus are used. The cork stoppers
are first impregnated with a suitable substance such as paraffin or
sodium silicate solution. This is done by submerging the prepared
stopper in the impregnating liquid in a heavy-walled bottle and evacuat-
ing until a considerable quantity of air has been removed from the cork.
Then when the vacuum is broken, liquid enters the cork. This may be
repeated.

Sometimes the various parts are connected by permanent glass seals. These are especially useful in the construction of apparatus for use at very low pressures, or for small-scale distillations.

8.22 Heating. Heating should be done by a liquid bath (A, Figure 8–4) in order that heat inflow be over a wide area, for, if heating is localized, bumping is more difficult to overcome. A thermometer should be suspended in the bath so that the temperature can be observed at

A — Liquid bath
B — Two-necked Claisen distilling flask
C — Capillary air tube
D_1 and D_2 — Thermometers
E — Condenser
F — Receiving flask

G — Manometer
H — Opening to air (Stopcock, or screw clamp)
I — Trap, to catch back flow from aspirator,
   and to act as a vacuum reservoir
J — Air leak for pressure regulation
K — To aspirator or pump
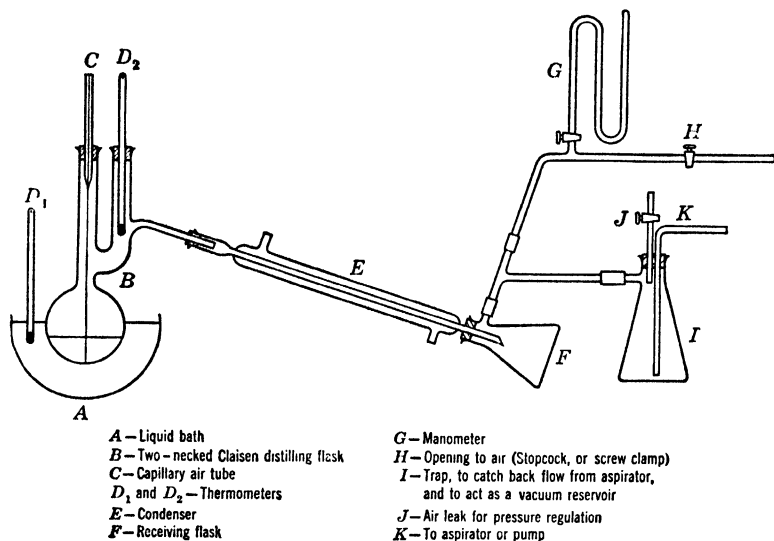
FIG. 8–4   Apparatus for Vacuum Distillation

all times. Heating baths are discussed in Chapter 7. A liquid bath need not be used with a radiant type of electric heater, which, properly controlled, is excellent for smooth distillation.

8.23 Controlling Bumping. Bumping is much worse when distillation is being done *in vacuo* than at atmospheric pressure, partly because dissolved gases are more quickly removed from the boiling liquid but largely because the volume increase when a bubble rises to the surface of the liquid is much greater when the pressure above the liquid is low. Bumping can be overcome successfully only by passing air or an inert gas such as nitrogen or carbon dioxide slowly through the boiling liquid. This is done by means of a glass tube, preferably capillary tubing, drawn down to a fine capillary thread and extending to the bottom of the flask (C, Figure 8–4). When properly made, it admits air in a very slow stream of fine bubbles (pinpoint in size) through the liquid when the system is pumped down at room temperature. It is highly important that air enter only extremely slowly, since boiling tempera-

tures are lowered when air is present. If the rate is too fast, the tube should be redrawn. A convenient flask is one having two necks, for example a Claisen flask (*B*, Figure 8–4).

Distillation should proceed smoothly and require little supervision. If it is uneven, the cause will be found to be one or more of the following: (1) uneven or excessive heating, (2) improperly constructed capillary air leak, (3) incomplete condensing, (4) solid matter in the boiler.
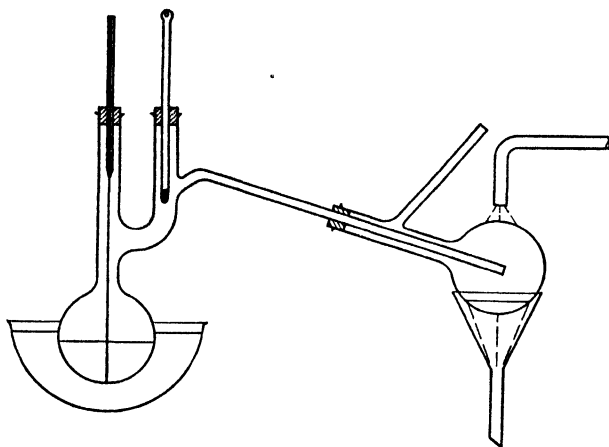
FIG. 8–5   Modification for Vacuum Distillation with Receiving Flask Acting as Condenser

8.24   Condensing. In the simpler apparatus (Figure 8–5) the receiver acts as the condenser. Cooling may be accomplished by directing a stream of water against the receiver. The side arm of the boiler must be long enough to extend well into the bulb of the receiver. When the condenser is of the Liebig type, it must be longer than in an ordinary distillation, because for the same rate of distillation the vapor velocity is many times greater in a vacuum distillation.

It is important to use a condensing surface so as to obtain a satisfactory rate of evaporation, even though a water aspirator is being used and the distillate is to be discarded. The disposal of large volumes of vapor characteristic of vacuum systems is much more rapid by condensation than by removal as a vapor through an aspirator.

8.25   Collecting the Distillate. The receiver (*F*, Figure 8–4) or adaptor is placed at the end of the condenser and is connected to the source of the vacuum. In general, the receiver is a distilling flask or a heavy-walled filter flask, since these will withstand the pressure and already have a side arm for evacuation. Light-walled flat-bottom flasks above 200 ml. capacity are liable to collapse.

8.26 Evacuating the System. This may be accomplished by either a water aspirator or an oil pump. The former has the advantage that it is inexpensive, has a large capacity, and may be used nearly down to the vapor pressure of water. It has the disadvantages of being limited to pressures above about 20 mm. and of permitting water to suck back into the system if the water pressure should decrease at any time. However, most aspirators are equipped with a valve to prevent this action. Nevertheless, a safety trap (Fig. 8–4, *I*) should be placed between the pump and the system to avoid any accident, since any previous contact with corrosive vapors may make the valve action erratic. If corrosive vapors are evolved during the distillation, the aspirator should be protected from these also (see the following).

Oil pumps have the advantage that pressures as low as 0.001 mm. may be obtained. However, this can be done only if the rest of the apparatus is sufficiently air-tight and the oil in the pump is free from volatile constituents. Usually, even when extreme care is taken in the setting up of the apparatus, the limiting pressure is about 0.01 mm. The oil pump has the disadvantages of being expensive and usually having a small capacity. For the latter reason it is imperative that there be no leaks. Some pumps have a large capacity so that they are able to cope with leakage. However, the minimum pressure obtainable with such pumps usually is about 0.01 mm. even under the best conditions.

It is imperative to protect the pump from any foreign vapor which might corrode the metal or increase the vapor pressure of the oil. A trap strongly cooled, as by Dry Ice or liquid air, to a great extent condenses undesirable vapors. Remaining traces of corrosive materials must not be allowed to reach the pump. These may be removed chemically. For example, acid vapors may be removed by *large* towers of soda lime or solid caustic. The efficiency of these absorbents depends on their being moist.

8.27 Measuring the Pressure. The pressure is measured by a manometer attached to the vacuum line adjacent to the receiver (G, Figure 8–4). Since some vapor passes through the vacuum line, the manometer is attached to the line by a T tube so that it will not be contaminated by any liquid condensing in the vacuum line. The pressure recorded at the manometer is not exactly the pressure of distillation, since there are pressure gradients which become more important, (1) the lower the pressure, (2) the smaller the tubing, (3) the greater the distance between the manometer G and the thermometer D_2, and (4) the greater the amount of air passing through the system.

Only the minimum of air should enter through the capillary C; otherwise, additional bad effects are: lowering the observed boiling temperature of the liquid, and incomplete condensation of the vapor.

8.28 Controlling the Pressure. If the distillation is being carried out at the minimum pressure of which the pump is capable, no special regulation is necessary. But, when the pressure must be higher than the minimum, it is controlled by permitting air to leak slowly into the system at the required rate (*J*, Figure 8–4). The control is simplest with systems of large volume, and thus it is often advantageous to place a large flask in the system between the manometer and pump to act as a "vacuum reservoir" (*I*, Figure 8–4). In general, the controlling air leak should be between the receiver and the pump. Often it is connected to the "vacuum reservoir." Control of pressure may be done automatically by a manometrically controlled air leak.

8.29 Breaking the Vacuum. Air should be admitted into the system *before* the action of the pump is stopped. The best procedure is to admit air at *H*, thus sweeping any organic vapors out of the manometer.

8.30 Changing Receivers. When the types of apparatus of Figures 8–4 and 8–5 are used, the vacuum must be broken from time to time when the receiver is changed. The heating bath should be removed first, to prevent heating of the liquid at atmospheric pressure. Although
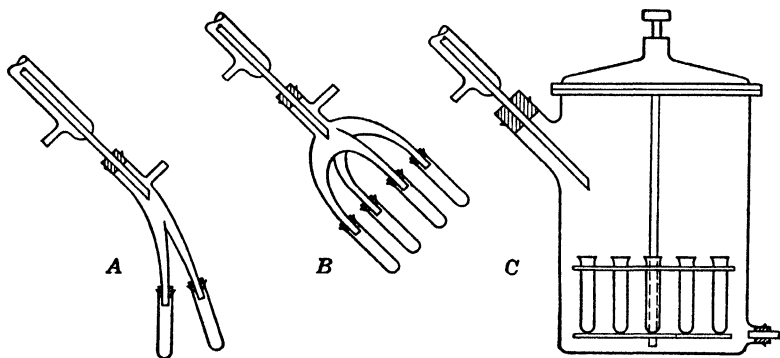
Fɪɢ. 8–6   Receivers for Making Cuts in Vacuum Distillation

the decomposition point may not be reached, the liquid boils violently when the pressure is again reduced. This may be so vigorous that liquid is carried over into the condenser, when the pressure is again reduced.

Since the receiver often is changed several times in a single distillation, it is convenient to use an apparatus that permits fractions to be taken without the necessity of breaking the vacuum. One method is to evacuate a system of more than one receiver and provide a means of directing the distillate into the receivers as in Figure 8–6, *A*, *B*, and *C*. The other is to provide a means of removing one receiver and evacuating a second without interrupting the distillation. An adapter for doing this is shown

in Figure 8–7. Here the condenser drains into A, and the vacuum line is connected at D, while F is open to the air.

When distillate is being collected in receiver B, stopcocks C, D, and E are open while stopcock F is closed. When the receiver is to be changed,
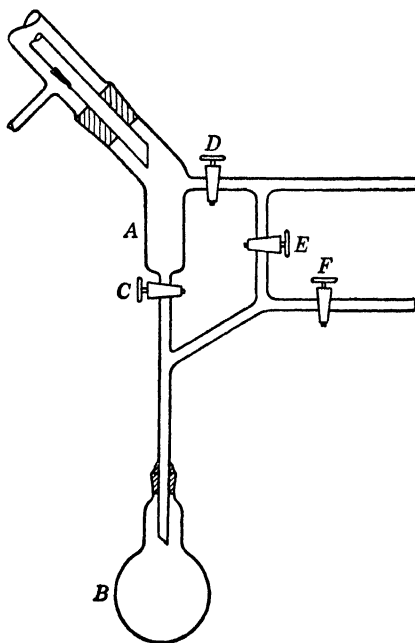
Fɪɢ. 8–7   Adaptor for Permitting Change of Receivers in Vacuum Distillation

stopcocks C and E are closed, and D is open. Now F is opened. Distillate continues to collect in A while the receiver, which now is at atmospheric pressure, is removed and replaced by a second. Then stopcocks D and F are closed, and E is opened. Just as soon as the pressure has dropped to the proper value, stopcock D is opened. Then C can be opened, and the distillate collected in the new receiver. This adapter has the disadvantage of leaving the distillate in contact with stopcock grease.

Chapter 9

FRACTIONAL DISTILLATION

Separations by distillation in general become more difficult as boiling points approach each other. In the distillation of two liquids which form ideal solutions, the first portions that are distilled are richer in the more volatile component than is the original mixture, and the last portions distilled are richer in the less volatile component. When the spread between boiling points is not wide, the enrichment of the first and last portions in the lower-boiling and higher-boiling component, respectively, is not marked. However, a satisfactory separation of the components of the mixture may be achieved, if the distillate is collected in several fractions and these are subjected to systematic redistillation, or if a fractionating column is used.

In spite of the increasing difficulty of separation, substances having boiling points as close together as 1° may be separated if the proper technique of fractional distillation is employed. However, some substances in certain mixtures, even though the boiling points lie far apart, cannot be separated by distillation methods. The question as to whether complete or only partial separation can be made depends on the way the vapor pressure of the solution varies with composition.

SECTION 9.1 FRACTIONATION OF IDEAL SOLUTIONS

9.11 Vapor Pressure of an Ideal Solution. Ideal solutions are those that obey Raoult's law. A quantitative expression of the law is given by Equation 9-1, where P is the partial vapor pressure of the solvent from the solution, N is the mole fraction of the solvent in the solution, and P_o is the vapor pressure of the pure solvent at that temperature.

$$P = NP_o \qquad (9\text{-}1)$$

As the mole fraction of the solvent decreases, owing to the presence of more dissolved material, the partial pressure of the solvent decreases proportionately. Relatively few solutions follow Raoult's law closely. Those that do are called perfect or ideal solutions, whereas the others are called imperfect solutions.

If two liquids form a perfect solution, they are miscible, the partial vapor pressure of each is proportional to its mole fraction, and the vapor pressure of the whole solution is the sum of the partial vapor pressures of the components. Pairs of substances that are very similar structurally and chemically are more likely to form perfect solutions than those that are not. The way in which the partial vapor pressures of each of two volatile components in a binary mixture depend on their compositions is illustrated by benzene and toluene. Figure 9–1 is a plot showing the
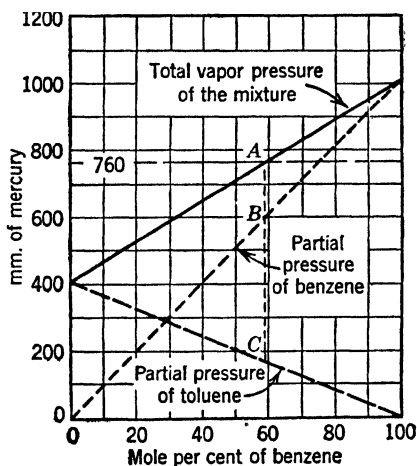
Fig. 9–1   Partial-Vapor Pressure Curves of Mixtures of Benzene and Toluene at 90°
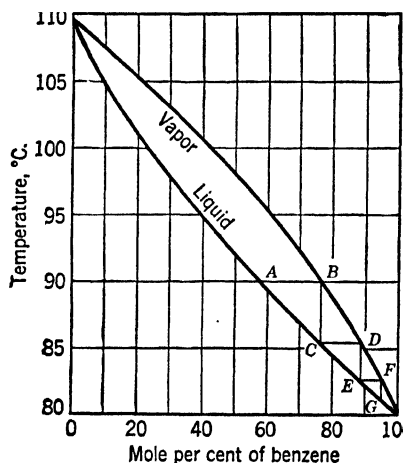
Fig. 9–2   Boiling-Point–Composition Curves of Mixtures of Benzene and Toluene at 760 mm.

total vapor pressure of benzene and toluene and the partial vapor pressures of benzene and toluene in all possible mixtures of these two liquids at 90°.

The straight-line character of the plots of the partial vapor pressures of benzene and of toluene in various mixtures of these two similar hydrocarbons at 90° (Figure 9–1) shows that these partial vapor pressures are proportional to the respective mole fractions and that the solutions are ideal. The partial vapor pressure of toluene goes linearly from 400 to 0 mm. as its concentration decreases, and the partial vapor pressure of benzene goes from 0 to 1000 mm. as its concentration increases. The total vapor pressure of the liquid goes from 400 to 1000 mm. as benzene replaces toluene. When the composition of the liquid is 58 mole per cent benzene and 42 mole per cent toluene, the total vapor pressure is 760 mm. This is point A on Figure 9–1. A solution of this composition has a boiling point of 90°C. The partial vapor pressure of the benzene is 580 mm.

(point B) and of the toluene is 180 mm. (point C).   Since the total pressure is 760 mm., the vapor which is in equilibrium with a solution containing 58 mole per cent benzene is 590/760 or 77 mole per cent benzene and 180/760 or 23 mole per cent toluene.   From this it is evident that the vapor is richer in the more volatile component, in this case benzene, than is the liquid.

At its boiling point, any mixture of benzene and toluene is in equilibrium with a vapor phase of a definite composition.   From data of a number of mixtures, two temperature–composition curves have been drawn, one for the liquid and one for the vapor phase, as shown in Figure 9–2.   Points A and B are the points that have been calculated for 90°.

9.12   Separation by Simple Distillation.   If a mixture of benzene and toluene is distilled from a simple distilling flask, the distillate will have the composition of the vapor in equilibrium with the liquid in the boiler.   Thus, for the mixture containing 58 mole per cent benzene, and boiling at 90°, the very first portion of the distillate will contain 77 mole per cent of benzene.   The composition of the liquid in the boiler becomes progressively richer in toluene as the distillation proceeds, owing to the fact that the distillate is richer in benzene at all times, relative to the liquid.   Thus, the composition of the very last portion of the distillate approaches that of pure toluene.

A very small amount of liquid approaching the composition of pure benzene can be obtained by a succession of distillations in the following way.   When a small amount of the mixture containing 58 mole per cent of benzene is distilled, the vapor contains 77 mole per cent of benzene B (Figure 9–2).   This can be condensed to a liquid, and, when it is heated, it begins to boil at 85°, as shown by point C.   The first vapor that comes over has the composition indicated by D, namely, 88 mole per cent.   This first small amount can in turn be condensed to a liquid, and, when this is heated, boiling begins at E, ca. 83°, and the vapor has the composition corresponding to F, ca. 95 mole per cent.   The operation can be continued until essentially pure benzene is obtained.   Thus it is possible by simple distillation to obtain both pure benzene and pure toluene, but the amounts recovered will be very small.

9.13   Systematic Refractionation.   It is possible to achieve satisfactory separation and recovery of the two volatile components by collecting the distillate in a number of fractions of small temperature range and subjecting these to a systematic refractionation in the following manner.   The first fraction is placed in the empty boiler and distilled until the distillation temperature reaches the upper temperature of the original first cut.   The distillate may be collected as two fractions in case a considerable amount distils at a temperature still lower than the

lowest previously observed. Then the original second fraction is added to the boiler, and distillation is continued until the upper temperature of the original second fraction is reached. The distillate that comes over in the range of the first fraction, or fractions, is added to that already collected, and that which comes over within the range of the original second cut is collected again as part of the new fraction of this temperature range. Then the original third fraction is added to the boiler, and the distillation is carried on till its upper temperature range is reached, cutting the distillate at the proper temperatures into the first, second, and third fractions. The process is continued until all original fractions have been distilled a second time. If considerable material distils above the previous upper temperature, this is collected as a separate cut (or cuts) at the upper end of the range.
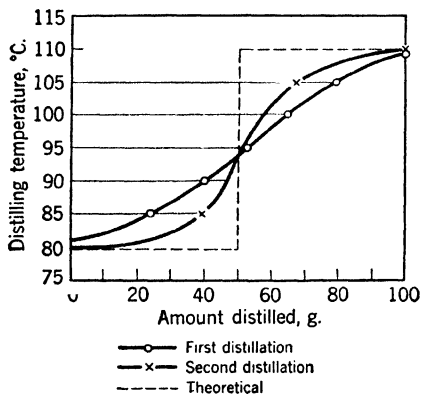
Fig. 9–3 Typical Distillation Curves of a Mixture of 50 g. each of Benzene and Toluene in 5° Cuts

Additional systematic refractionations are performed until separation is satisfactory. The temperature of the first cut should be lowered, if possible, and that of the last cut should be raised, and the range of both should be narrowed so as to improve the purity of the first and last fractions.

Figure 9–3 shows how a 50–50 mixture of benzene and toluene separates into 5° fractions by this procedure. In the first distillation about one fourth of the total comes over in the first 5° cut, and the liquid is not pure at any time, since the boiling point is above that of pure benzene, namely, 80°. In the second distillation about 40% is in the first 5° cut, and it is purer. If the separation had been complete, the distillation curve would have followed the dotted line.

9.14 Fractionating Columns. A fractionating column is an apparatus that increases the degree of separation when a mixture of volatile components is distilled. Of the several types shown in Figure 9–4, the simplest to discuss is the bubble plate column *H*. This is constructed so that liquid collects at each plate, and the rising vapor is forced to bubble through the liquid at each plate.

To simplify the discussion, it may be assumed that the column is empty, that it is cold, that it is completely insulated, and that no liquid flows down from any plate; also, that the amount of liquid in the boiler

is so large that it changes little in composition during the distillation. At the start of the distillation, liquid condenses on the plates, since the apparatus is cold.   If the original composition is 58 mole per cent

Glinsky tube	Young tube	Vigreux tube	Hempel tube and column
A	*B*	*C*	*D*

Cold-finger reflux	Total reflux with take off	Flask for stripping off solvent	Section of bubble plate column
E	*F*	*G*	*H*
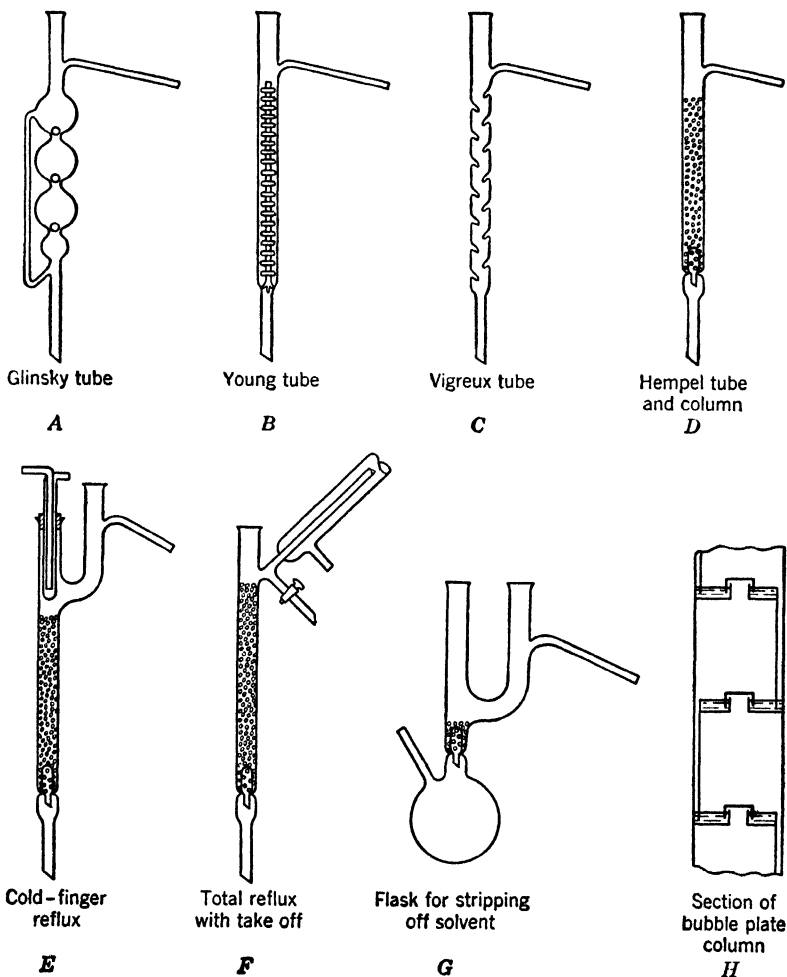
Fig. 9–4   Fractionation Apparatus

benzene, the composition at the first plate is again 77%, *C* (Figure 9–2); that at the second plate is indicated by *E*; and so on.   There is a drop in temperature between one plate and the next higher one.   Thus the column acts like a serial bank of distilling flasks, giving a theoretical separation equivalent to that achieved by as many distillations from distilling flasks as there are plates in the column.   If there are enough

plates, the composition of the first vapor that issues from the top of the column approaches that of pure benzene.

As the distillation proceeds, vapor ascending from the boiler bubbles through the cooler liquid on the bottom-plate. Equilibration of the vapor and liquid at the plate results in the condensation of a part of the higher-boiling component of the vapor, and the vaporization of essentially the same molar quantity of the lower-boiling component of the liquid. This causes the liquid to become richer in the higher-boiling component and the vapor to become richer in the lower-boiling component. At the same time the temperature of the liquid on the plate rises, for the boiling point rises as the proportion of the higher-boiling component increases. This heating effect leads to a gradual decrease in the efficiency of the column, for in time all the plates reach the temperature corresponding to A (Figure 9–2). Then the composition of the vapor leaving the column is that indicated by B.

The efficiency of the column is greatly enhanced by returning some of the final product, in the form of liquid, to the top of the column, and permitting all but a small portion of liquid at the plates to flow down to the plate below. The easiest way to return liquid to the top of the column is to use a reflux condenser at the top of the column. This causes a general flow of liquid down the column, and an enrichment at the plates in the lower-boiling component. It is thus possible to maintain the composition of the liquid on the lowest plate at the point C (Figure 9–2) so that the vapor, if complete equilibrium is assumed, issues with the composition of D. The other plates perform similarly. Then there is a temperature gradient up the column, which continues to function as a succession of distillations from distilling flasks. It is even possible to increase the concentration of the lower-boiling component at the lowest plate above that of the vapor issuing from the boiler, by returning a sufficiently large amount of liquid to the column.

The ordinary laboratory fractionating column does not hold liquid on plates, as does the bubble plate column, but provides extra surfaces on which vapor may come in contact with the liquid. As the vapor ascends, it comes in contact with the cooler liquid descending, and in the attempt to attain equilibrium the vapor loses the higher-boiling component and acquires the lower-boiling component, just as in the case of the bubble plate.

The efficiency of a fractionating column in achieving separations depends on the following: (1) amount of contact between vapor and liquid, (2) amount of reflux, (3) rate of distillation.

The amount of contact between vapor and liquid is determined by the length of the column, the diameter of the column, and the type of packing. The function of the packing is to provide surface area for contact

between the vapor and liquid phases. Also it serves to break up and prevent stream-line flow of vapor or liquid. These purposes are accomplished by Glass balls (Glinsky tube, A, Figure 9–4), glass plates (Young tube, B), indentations in the side of the tube (Vigreux tube, C), and more satisfactorily by various types of packing, such as beads, rings, coils, and helices. Usually these are of glass, but sometimes, as in industrial operations, they are of metal.

Refluxing preferably should be concentrated at the top of the column, in order that the returning liquid may run the entire length of the column. A cold finger condenser is quite satisfactory and is used in connection with the Claisen-type head. In the total-reflux type F, all the vapor is condensed, and the desired amount of distillate is allowed to flow into the receiver. The control of the reflux ratio is easier here. **The reflux ratio** is the ratio of the amounts of liquid returned at the top of the column to the amount distilled. Usually the reflux ratio should be at least 5.

Often columns are used without reflux condensers, but they depend on some condensation along the length of the column resulting from heat losses through the side of the column. Also, heat losses interfere with maintenance of equilibrium, since there is a temperature gradient from the center of the column to the outer wall, when the only gradient should be a vertical one. Vapor condenses along the outer wall, causing a composition gradient in a horizontal direction, when it should be only in a vertical direction. Heat losses can be reduced by wrapping the column with insulating materials or, better, by providing an evacuated jacket. Sometimes the column is heated by means of resistance wire, in order to balance heat losses.

The rate of distillation should be slow enough to allow sufficient time for equilibrium to be established between vapor and liquid. The efficiency of the column increases as the rate of distillation decreases. If the rate of distillation is too fast, flooding of the column occurs, and liquid is forced up the column instead of draining down. Thus, equilibrium conditions are better approximated by having the column insulated and provided with a total reflux condenser F (Figure 9–4), and by distilling slowly.

9.15   Selection of Fractionation Apparatus. The type and size of column and the size of boiler depend on a number of factors, among them: (1) the boiling-point separation, (2) the distilling temperatures, (3) the amounts to be distilled. When the boiling-point separation is narrow, a more efficient column must be used than when it is wide. If the distilling temperatures are high, insulation of the column may be necessary; otherwise, heat losses may cause complete condensation of the vapor. When small amounts are being distilled, the capacity of

boiler and column should be small; otherwise, too much material is lost at the end of the distillation. The holdup for various packings increases in the order

$$\text{Beads} < \text{helices} < \text{rings}$$

When a small amount of higher-boiling liquid is to be recovered from a large volume of low-boiling solvent, the desired higher-boiling product, after distillation of the bulk of the solvent, should be distilled from a flask suitable to the amount of liquid. To avoid transferring, the solution may be allowed to flow slowly into a small boiler of proper size while the more volatile solvent is stripped off through a fractionating column. An apparatus especially designed for stripping off a volatile solvent is flask G (Figure 9-4). It is important that the distilling temperature be essentially the boiling point of the solvent, for the loss of product may be substantial, even if the solvent distils only 2° or 3° too high.

SECTION 9.2 FRACTIONATION OF NONIDEAL SOLUTIONS

9.21 Nonideal Solutions of Miscible Liquids. In many solutions of miscible liquids the partial vapor pressures of the components are
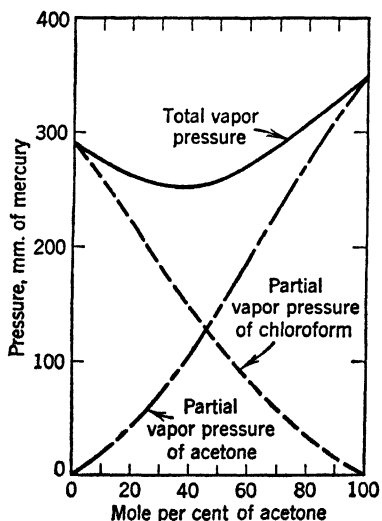
FIG. 9-5 Partial Vapor-Pressure Curves of Mixtures of Acetone and Chloroform at 35°
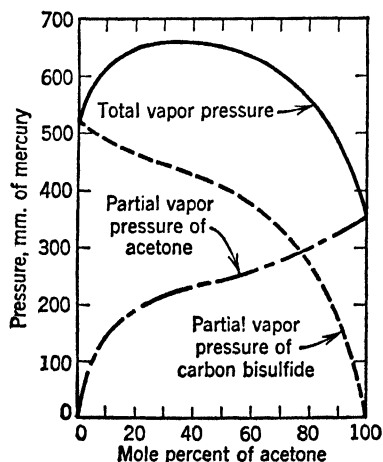
FIG. 9-6 Partial Vapor-Pressure Curves of Mixtures of Acetone and Carbon Bisulfide at 35°

not linear functions of their concentrations at constant temperature. When the partial vapor pressures of each are below the Raoult's law

values, usually the total vapor pressure at a given temperature has a minimum value, and, when the partial vapor pressures of each are above the Raoult's law values, usually the total vapor pressure at a given temperature has a maximum value, at some particular composition.

Mixtures of acetone and chloroform at a temperature of 35° exhibit a minimum in the total vapor pressure at 40 mole per cent acetone (Figure 9-5). Mixtures of acetone and carbon bisulfide, at a temperature of 35°, exhibit a maximum in the total vapor pressure at 35 mole per cent acetone (Figure 9-6). The boiling-point–composition curves at 760 mm. pressure for these two pairs of compounds are shown in Figure 9-7, where the upper curve represents the composition of the vapor and the lower that of the liquid. Among the mixtures in which the partial vapor pressures of the components are less than for an ideal solution, there is one that has a maximum boiling point, and, among those where the partial vapor pressures are greater, there is one that has a minimum boiling point. The mixture that has a maximum or minimum boiling point is called an azeotropic mixture.

A - Mixtures of acetone and chloroform
B - Mixtures of acetone and carbon bisulfide
––––– liquid   ──── vapor

Fig. 9-7 Typical Boiling-Point–Composition Curves of Pairs of Liquids Which Form Azeotropic Mixtures

A large number of azeotropic mixtures are known. Such mixtures are encountered frequently in laboratory work in organic chemistry. Azeotropic mixtures of maximum boiling point are much less common than those of minimum boiling point, although a few are well known in inorganic chemistry, such as those between water and the hydrogen halides.

The curves of Figure 9-7 are useful in showing how mixtures of acetone and chloroform and mixtures of acetone and carbon bisulfide behave when distilled. Each azeotropic mixture distils unchanged at a constant temperature. The composition of the vapor is the same as that of the liquid. Thus, these constant-boiling mixtures behave as pure liquids on distillation. Other mixtures act as though they were ideal solutions made up of two components, one being a pure compound and the other the azeotropic mixture. Thus, mixtures of acetone and chloroform con-

taining less than 36 mole per cent acetone yield pure chloroform and the azeotropic mixture on fractionation, and mixtures containing more than 36 mole per cent yield pure acetone and the azeotropic mixture. In this system a pure component distils first.

Mixtures of acetone and carbon bisulfide, other than the constant-boiling mixture, likewise can be separated by fractional distillation into the azeotropic mixture and a pure compound, but in these cases the mixture distils first.

9.22 Immiscible Mixtures. If totally insoluble mixtures are distilled, the composition of the vapor does not depend at all on the composition of the mixture. Each component exerts the same vapor pressure that it has when alone, and the boiling temperature is below that of the lower-boiling substance. The distillate is composed of the two components in the molal ratio corresponding to the respective vapor pressures at the distilling temperature. Distillation of immiscible liquids is discussed in more detail under Steam Distillation, Chapter 10.

9.23 Partially Miscible Liquids. When the components of a mixture are only partially miscible, their partial vapor pressures are much higher than for ideal solutions. Such a mixture constitutes a minimum constant-boiling mixture, as in the case of a pair of miscible liquids whose partial pressures exceed the Raoult's law values. Whenever two liquid phases are present, the partial vapor pressure of either of the components is the same from both phases, even though the phases are quite different in composition.

A typical example is the system of water and n-butyl alcohol. Figure 9–8 shows the partial pressure of each component at 92.5°. Two phases are present in all those mixtures in which the percentage of alcohol is between 8 and 69. Over this entire range of composition the partial vapor pressure of water is 540 mm., and that of n-butyl alcohol is 220 mm.

Figure 9–9 is the boiling-temperature–composition curve of the system, water–n-butyl alcohol, at 760 mm. The vapor in equilibrium with the two-phase liquid system is composed of 62% n-butyl alcohol and 38% water, and the mixture of this composition, which likewise consists of two phases, is a constant-boiling mixture and distils unchanged at 92.6°. On efficient fractional distillation of any other mixture, constant-boiling mixture is obtained first, followed by water if the alcohol content of the original mixture was less than 62%, and by n-butyl alcohol if it was greater than 62%.

Complete removal of water from aqueous butyl alcohol, with only slight loss of alcohol, can be accomplished by a combination of distilla-

tion and phase separation.   The two-phase distillate containing butyl alcohol is separated, and the alcohol phase is returned to the boiler and redistilled until all water is gone.   Thus the only loss is that correspond-
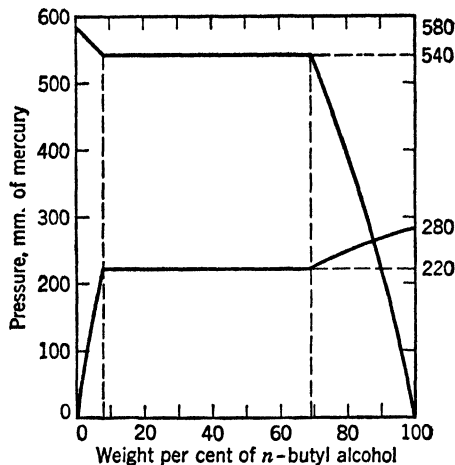
FIG. 9–8   Partial Vapor-Pressure Curves of Mixtures of Water and n-Butyl Alcohol at 92.5°

Field A. One phase, vapor
Field B. One phase, liquid
Field C. One phase, liquid
Field D. Two phases, vapor and liquid
Field E. Two phases, vapor and liquid
Field F. Two phases, liquid and liquid
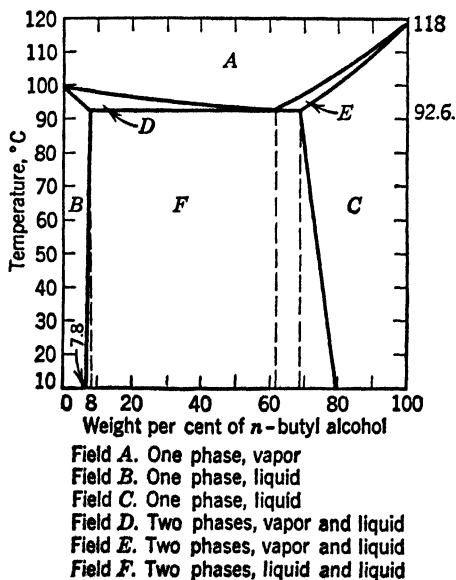
FIG. 9–9   Phase Diagram, Including Boiling-Point–Composition Curves, of n-Butyl Alcohol–Water System at 760 mm.

ing to the alcohol dissolved in the separated water. If desired, this aqueous phase also could be distilled, yielding more of the azeotropic mixture. Distillation is one of the easiest ways of freeing many volatile organic compounds from water.

Mixtures usually encountered in organic laboratory work are more complicated than the two-component system here discussed. Often three components are present, and sometimes even more. The practical methods of handling these are similar.

SECTION 9.3   FRACTIONAL DISTILLATION AT REDUCED PRESSURE

Vacuum fractionation is conducted as an ordinary fractionation except that the same precautions are observed as for vacuum distillation (Chapter 8). However, here the vapor is more dilute and hence passes through the column at a greater velocity, thus increasing the tendency toward flooding.

Usually better separation of two substances by fractional distillation may be achieved at a lower pressure. This is exemplified in the separation of n-octane and bromobenzene (Figure 8–2). At 126°, which is the boiling temperature of n-octane at 760 mm., the vapor pressure of n-octane is 2.3 times the vapor pressure of bromobenzene, whereas at 32° the vapor pressure of n-octane is 3.3 times that of bromobenzene. This greater spread of the vapor pressures at lower pressures is characteristic of all ideal solutions of substances that conform to Trouton's rule (Equation 8–4).

In case one of the substances of the pair being separated by distillation does not conform to Trouton's rule, it is possible for the spread of vapor pressures to be less at lower temperatures. In this respect, o-xylene and m-xylene are interesting. At 140° the vapor pressure of o-xylene is 690 mm., and that of m-xylene is 785 mm. At progressively lower temperatures the spread becomes narrower until at 60° both have the same vapor pressure, namely, 61 mm. At still lower temperatures the spread increases, but in the opposite direction, for at 40° the vapor pressure of o-xylene is 23.7 mm., and of m-xylene, 19.5 mm. Thus m-xylene has the higher vapor pressure at 140°, and o-xylene at 40°.

Vacuum fractionation may be useful also in the separation of components of azeotropic mixtures, for the composition of the azeotropic mixture will change with pressure, and a better separation may be possible at reduced pressure. Thus, absolute alcohol may be obtained from 96% alcohol by first fractionating at pressures below atmospheric, followed by fractionating at atmospheric pressure, because the azeotropic mixtures at the lower pressures are richer in alcohol.

Experiment 9–1   Fractional Distillation of Methanol and Water
(Note 1)

The purpose of this experiment is to acquaint the student with the methods used in separating volatile substances from each other by distillation. The performance of different types of apparatus and the function of fractionation by cuts should be observed and understood. Each student, as advised by the instructor, uses a different type of apparatus such as the ordinary distilling flask or other apparatus described in this chapter. Some will use distilling tubes that are similar but are modified by use of a reflux condenser or by variation in packing.

Set up the apparatus, using a flask of about 300 ml. capacity, making connections with properly fitting cork stoppers (Note 2). The flask should be 1 to 2 cm. above the burner, which should be adjustable so as to give a small flame.

Record in your notebook all pertinent data regarding the apparatus (Note 3). Record also the boiling points and mutual solubilities of methanol and water. Prepare ahead of time in your notebook a table in which you can record all desired data *as the experiment is being performed* (Note 4).

Place a mixture of 100 ml. of water and 100 ml. of methanol in the flask and some material to act as a boiling aid, namely, one or two ebullition tubes or a few pieces of porous tile, not soft burnt (2 to 5 mm.). Heat to boiling with the bare flame, and as soon as liquid flows from the condenser regulate the flame (Note 5) so that liquid flows at a *constant rate* of 2 drops per second, *irrespective of the type of apparatus* (Note 6).

Collect the distillate in a graduated cylinder. Read and record the distilling temperature every 10 ml. or oftener. Be prepared to transfer the distillate to suitable flasks (two 100-ml. flasks for the first and last cuts and three smaller for the intermediate cuts) so as to obtain the following cuts (fractions): (1) up to 70°; (2) 70°–75°; (3) 75°–85°; (4) 85°–95°; (5) 95°–100° (?). Record the volume of each fraction, the volume of the final residue, the time elapsed during the distillation, and any loss.

In case the separation of methanol and water is not satisfactory, repeat the distillation in a systematic manner as discussed. Keep a complete record (Notes 4, 7, and 8).

Finally, draw a plot of temperature as ordinate against total volume of distillate. In case more than one distillation was carried out, draw the curves on the same plot. On a second plot draw for comparison your initial curve and those obtained by two other students using other types of apparatus. Be sure to give them credit by including their

names. Discuss the results from the standpoint of efficiency, time, and per cent recovery.

Draw a molar composition–temperature diagram of a mixture of methanol and water for the liquid and vapor states at atmospheric pressure (Note 9). Show on this diagram the approximate composition of the distillate obtained by distilling 1% of the mixture without any fractionation and then repeating on the distillate.

Notes

1. These two compounds are selected because separation by distillation is not complicated by the existence of an azeotrope. Although it is not necessary to correct for barometric pressure, since it is essentially constant during the experiment, its effect on the boiling point may not be negligible.

2. Refer to Experiment 3–1, Note 4, in regard to making good connections with cork stoppers. If a distilling flask is used, refer to Fig. 7–1; guard tube H is unnecessary, and the adapter can be omitted.

3. If a distilling tube is used, include the following: dimensions of the tube, nature and amount (length) of packing, type of head, and type of reflux condenser, if any.

4. In any fractional distillation of two or more volatile substances it is desirable to record at frequent intervals the distilling temperature and the volume of the various fractions, so that the total volume distilled can be plotted against the temperature. It is desirable to record also all the other variable factors such as time, rate of refluxing (if any), rate of distillation, and reflux ratio (if any). The following is suggested:

Clock Time	Therm. Reading, °C.	Drops per sec.		Reflux Ratio	Fract. No.	Vol. in Fraction, ml.	Total Vol., ml.	Time, min.	Loss, ml.	Remarks
		Reflux	Distln.							

If it is necessary to repeat the distillation, add another column in order to record the cut added.

5. Variations in the rate of heating due to drafts of air in the room may be minimized by keeping the flame close to the flask and/or by protecting the flame with screens.

6. The relative efficiencies of the different types of apparatus can be determined only if the rate of distillation is alike in all cases.

7. In case the separation is still not complete, a third distillation is recommended so as to emphasize the value of refractionation by cuts. The limits of the first and last cuts should be narrowed, preferably to ca. 2°, so as to increase the purity of these fractions.

8. In case cork stoppers are badly stuck, remove these by cutting so as not to break the apparatus when dismantling.

9. See *International Critical Tables*, 1928, Vol. 3, p. 309, McGraw-Hill Book Co., and Cornell and Montenna, *Ind. Eng. Chem.*, **25,** 1331 (1933).

Questions

1. Is an electric hot plate as satisfactory as a flame in this experiment? Explain.

2. What is the advantage or disadvantage of heating with an oil bath which in turn is heated by a flame?

3. Explain the function of an ebullition tube or a porous chip.

4. What is the function of the cold-finger condenser?

5. Explain its effect on the efficiency of the apparatus.

6. Explain why liquid continually flows back into the boiler from a fractionating column that does not have a reflux condenser.

7. Does this refluxing liquid have any effect on the distillation?

8. Is it possible to effect a reasonably complete separation of methanol and water by distillation of a 50% solution?

9. Ditto, ethanol and water?

10. What is meant by the reflux ratio?

11. What effect does an increase in the reflux ratio have on the degree of separation? Compare the results of two students who used the same type of apparatus.

12. How do you account for this effect?

13. Explain the exceptions to Trouton's rule in Table 8-1.

14. From the data of the references in Note 9 and the vapor pressure of pure methanol, calculate the magnitude of the deviation from Raoult's law.

Chapter 10

STEAM DISTILLATION

When a volatile substance is distilled with water, the substance is said to be steam-distilled if water comes over in the distillate. Steam distillation is not feasible if the substance reacts rapidly with water. It is especially useful under one or more of the following conditions: (1) when the presence of solid matter makes ordinary distillation, filtration, and extraction impractical, as for example in Experiment 33–1, the Preparation of Aniline; (2) when the presence of tarry matter makes extraction with an organic solvent messy and inconvenient, as in Experiment 35–2, the Preparation of Phenol; (3) when the volatile product is a solid, for then the water in the condenser serves to keep the condenser from clogging; (4) when the desired substance boils much above 100° and decomposes at its boiling point; (5) when separation from a volatile impurity can be accomplished better at reduced pressure, as the separation of bromobenzene from p-dibromobenzene in Experiment 30–1, the Preparation of Bromobenzene.

Steam distillation may in some cases take the place of vacuum distillation, and has the advantage of greater convenience.

SECTION 10.1 PRINCIPLE OF STEAM DISTILLATION

If the substance is insoluble in water, the mixture boils when the sum of the vapor pressures of the components is equal to atmospheric pressure. This is below the boiling temperature of both substances. The distillate is composed of the two components in molar proportions relative to their vapor pressures at the temperature of distillation. Though the vapor pressure of the substance being steam-distilled may be much smaller than that of water, it still may constitute an appreciable fraction of the distillate, since its molecular weight and, therefore, its molecular volume are much greater than those of water. Thus, although the vapor pressure of water at 100° is 42 times that of p-dibromobenzene which boils at 218°, the weight of water in the distillate is only 3 times the weight of the dibromobenzene, because the molecular weight of the latter is 235.

If the substance has a limited solubility in water, the procedure is modified by continuing the distillation after the distillate becomes a single phase, in order to make sure that all of the material has distilled. However, the volume of the single-phase distillate should be limited, to avoid subsequent difficulty of recovering the product from a quite dilute aqueous solution. It is well to collect separately the single-phase distillate, to avoid dissolving the organic phase. The dissolved product may be recovered from the aqueous phase by extraction with a suitable solvent.

SECTION 10.2   APPARATUS

A typical setup for steam distillation is shown in Figure 10–1, when steam is generated by the worker. This consists of the steam generator
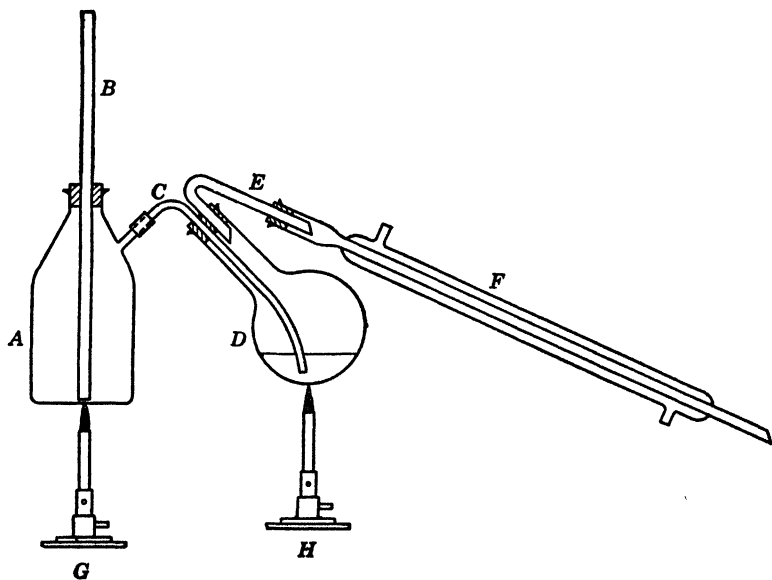
FIG. 10–1   Apparatus for Steam Distillation

A, preferably a metal can, a tilted flask D, a long condenser F, and two burners G and H. The generator must be provided with a safety tube leading to the bottom of the vessel. The exit tube C should reach to the bottom of D, so that the incoming steam will keep the contents well agitated, thus helping to maintain equilibrium between the phases. Also, C should not be smaller than 7 mm.; otherwise, its capacity is so small that the operation consumes too much time. Flask D preferably should not be more than half filled with liquid. Tilting of D serves to

decrease the splashing of liquid into the exit tube E and to keep that which has splashed from being carried over into the condenser. Tube E should be as short as possible before bending over, to minimize refluxing and should be about 1 cm. wide, to permit splashings to flow back into D and to prevent excess pressure in D. After bending over, E may be long, to permit some cooling by the air before entering the condenser. The condenser F should be long, since the heat of vaporization of water is high, and the distillation rate should not be limited by the capacity of the condenser. The flame from the burner H need only be large enough to compensate for radiation losses.
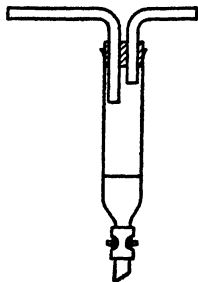
FIG. 10–2 Trap for Removing Water from Steam Line

Steam when taken from a steam line usually is mixed with water. This must be removed by means of a suitable trap. Figure 10–2 shows a simple apparatus, consisting of a large straight adaptor. Steam enters and leaves at the top, and the water is drawn off from time to time through a rubber tube closed with a clamp.

When the steam is turned off, air must be admitted into the trap; otherwise, liquid from the boiler is drawn into the trap. The trap should not be lower than the flask; otherwise, admitting air to the trap, once liquid has started to flow from flask to trap, does not break the siphon.

SECTION 10.3   SUPERHEATED STEAM DISTILLATION

When the substance has a very high boiling point and therefore such a low vapor pressure at 100° that the amount that distils is insignificant, distillation often can be accomplished by superheating the steam, that is, by raising it to a temperature above 100° before passage through the substance, which also should be above 100°. Since the latter then has a greater vapor pressure, the distillate has a greater proportion of the substance. The partial pressure of the substance is then its vapor pressure at the higher temperature, whereas the partial pressure of water is the difference between this value and atmospheric pressure, rather than the vapor pressure of water at the higher temperature. The superheated steam acts as an inert gas passed through the substance and evaporates it much as a stream of air causes the evaporation of a volatile liquid. However, steam has the advantage that it can be condensed completely, whereas the inert gas would carry away with it some of the substance

partly as vapor, and partly as finely divided particles of the condensed phase (fog or smoke).

Steam may be superheated by passing ordinary steam through a coiled metal tube or a flat metallic "steam superheater" which is heated by a flame. However, before the metal is heated, steam should be flowing through the apparatus; otherwise, the metal, especially if copper, may be badly oxidized. It is desirable to place a thermometer in the superheated steam line in order to know the temperature. The distance from superheater to flask should be the minimum.

SECTION 10.4 CODISTILLATION

Sometimes neither steam nor superheated steam is satisfactory, for one or more of the following reasons: (1) The substance reacts with steam; (2) the boiling point of the compound is very high; (3) the compound is very soluble in water. Steam distillation then can be replaced to advantage by codistillation, that is, distillation with a liquid which when cold dissolves little or none of the substance. Preferably the liquid employed should have a boiling point near that of the compound, and the molecular weight should be less. For example, anthracene can be distilled with mercury. Also, many high-boiling compounds can be codistilled with a suitable petroleum fraction.

Chapter 11

SUBLIMATION

Sublimation consists in the conversion of a solid directly into a vapor and the vapor directly back into the solid without passage through a liquid state. This process may be used in the laboratory to purify those solid compounds that have sufficiently high vapor pressures. The conversion of the vapor directly into the solid is the important step. The advantage of sublimation lies in obviating contact of the crystals with any liquid so that the product is obtained in the form of pure crystals which have not been in contact with any liquid. Sometimes substances that can be distilled without difficulty are sublimed instead, for this reason.

SECTION 11.1 VAPOR PRESSURE OF SOLIDS

The vapor pressure of a solid increases with temperature in much the same way that the vapor pressure of liquid does (Equation 8–1). Equation 11–1 shows the dependence of the vapor pressure of a solid on temperature.

$$d \ln p/dT = \Delta H_s/RT^2 \qquad (11\text{–}1)$$

Here ΔH_s is the molal heat of sublimation of the solid.

11.11 Sublimation of Camphor. Figure 11–1 is the vapor-pressure–temperature diagram for camphor. The line AT between the regions labeled solid and vapor represent the vapor pressure of the solid at the corresponding temperature. The line BT between the regions labeled liquid and vapor represents the vapor pressure of the liquid. The line CT between the regions labeled solid and liquid represents the melting point at various pressures. The point T (179° at a pressure of 370 mm.) is the triple point where the solid, liquid, and vapor are all at equilibrium with each other. This is the melting point of camphor at a pressure of 370 mm.

If camphor is heated under normal conditions of 1 atmosphere, it melts at 179°, and the liquid boils at 208°. If pure camphor vapor at atmospheric pressure is cooled, liquid is first formed, and on further cooling this solidifies, as shown by passing from left to right along the line DE, at 760 mm. Liquid is first formed at all pressures above the

triple-point pressure of 370 mm. However, at all pressures lower than 370 mm., camphor may pass from solid to vapor, and *vice versa*, without going through a liquid state, as shown by passing along the line *FG*.

Thus sublimation may be carried out with camphor at pressures below 370 mm. Also, it may be done at total pressures above 370 mm., in the presence of some gas, for example, air, provided the partial pressure of the camphor vapor does not exceed 370 mm. Thus sublimation is possible at atmospheric pressure. Suppose for example that the temperature of solid camphor is raised to 170°. The pressure exerted by the camphor vapor then is 300 mm., irrespective of whether or not air is present. The solid and vapor are in equilibrium. If part of the surface of the containing vessel is cooled, say to 25°, solid camphor will be deposited because the pressure of camphor vapor in equilibrium with the solid at 25° is 0.7 mm. Thus camphor is carried, partly by diffusion and partly by convection, from the region of higher vapor pressure to the one of lower vapor pressure, from the hot region to the cold region, without passing through the liquid state. The vapor deposits on the crystals already formed, and these may grow until they

FIG. 11–1   Vapor-Pressure–Temperature Diagram of Camphor

are quite large. The process may take place in a vacuum or in the presence of an inert gas. Under the latter conditions the sublimation process is much slower since the gas molecules hinder the diffusion of camphor molecules. Thus in a stationary system air lowers the rate of sublimation. Generally the process is very much slower than distillation.

The rate of sublimation can be increased by using a stream of inert gas to carry the vapor to the cold surface. In fact, the camphor can be heated much above its melting point, provided the rate of passage of the gas is sufficient to keep the partial pressure of camphor in the gas stream below 370 mm. Then, when this is cooled sufficiently, camphor vapor will pass directly into camphor solid. If the cooling is done rapidly, the crystals are small, owing to the rapid rate of separation.

Also, the crystals are quite pure because the gas carries off impurities.

The disadvantage of sublimation in a stream of gas is a possible loss of material because the outgoing stream of gas will be saturated with vapor of the solid at the lower temperature, and in addition the solid, if in a very fine condition, may not be removed completely from the gas.

11.12 Other Substances That Sublime Easily. Substances that may be sublimed readily are limited to those having an appreciable vapor pressure in the solid state. In Table 11–1 are listed the vapor pressures of some solids at their melting points.

TABLE 11–1

Vapor Pressures of Some Solids at Their Melting Points

	Melting Point, °C.	Vapor Pressure at Melting Point, mm.
Hexachloroethane	186	780
Camphor	179	370
Iodine	114	90
Anthraquinone	286	14
Naphthalene	80	7
Benzoic acid	121	6

SECTION 11.2 PROCEDURES FOR SUBLIMATION

In carrying out a sublimation, one must bear in mind that the condensing surface becomes coated with the solid which does not drain itself automatically, as does a condensing liquid, but must be removed mechanically. Therefore, as large a condensing surface as possible should be used, and the sublimate should be easily accessible for removal. The condensing and evaporating surfaces should be close together. The solid should be well dried; otherwise moisture condenses on the sublimate.

Various types of sublimation apparatus are illustrated in Figure 11–2. *A* shows two watch glasses clamped together with a piece of perforated filter paper between them. The substance to be sublimed is placed on the lower glass which is heated on a sand bath. Direct-flame heating is avoided because of the extreme difficulty of avoiding overheating. The solid sublimes onto the cooler upper glass and is prevented from falling back into the impure material by the filter paper. If much material is to be condensed, it may be necessary to cool the condensing glass with a wet cloth.

B shows a funnel inverted over an evaporating dish. A piece of filter paper may be used here also. Slight suction may be applied at the funnel

stem in order to sweep the vapor into contact with the walls at a lower temperature.   In this case a small plug of cotton should be inserted in the stem to prevent the air from carrying particles away.   The glass funnel may be replaced to advantage by a Buechner funnel.

C shows a flask set in a beaker, preferably one without a spout.   The flask may be filled with cold water and thus serves to cool the vapor.
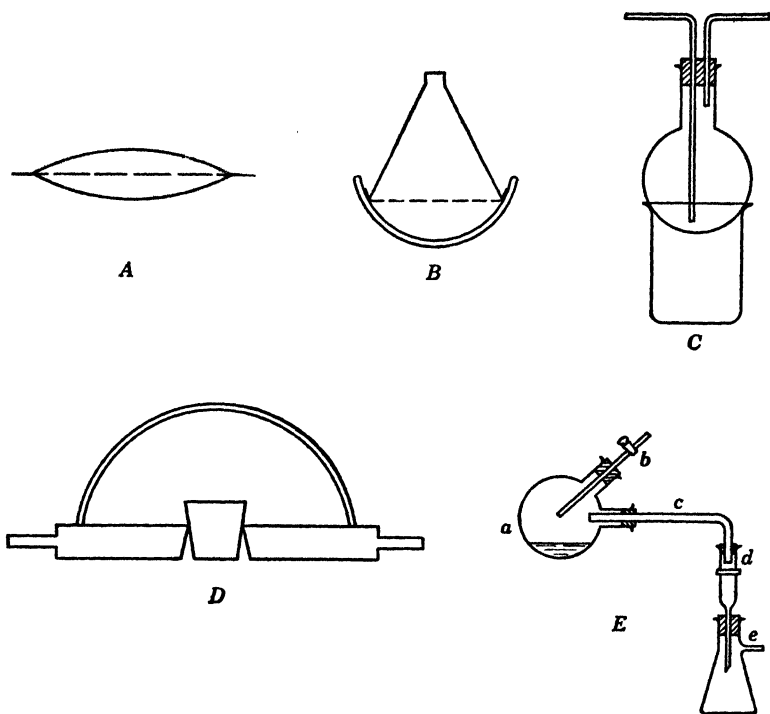
FIG. 11-2   Sublimation Apparatus

This method serves well for purifying an easily volatilized solid, for example camphor, iodine, or p-benzoquinone (Experiment 38-1).   D shows a crucible supported in a round flat metal condenser through which water circulates.   The whole is covered by a glass dome.   The material sublimes out of the crucible onto the cold surface.

E shows a type of apparatus that may be used for sublimation in a stream of air, which may be at atmospheric or reduced pressure.   A two-necked flask a is equipped with a narrow inlet tube b with stopcock (or other control) and a condenser tube c about 15 mm. in diameter. This is fitted to a Gooch crucible d, preferably a sintered-glass crucible, in the usual tube and suction flask e.   A well-fitting filter paper is placed

on top of the filter plate to collect any sublimate carried by the air stream.   The solid that has collected may be removed from time to time.

For high-melting solids, as for example 2-bromoanthraquinone (Experiment 38–3) a low pressure is necessary.   The pressure is controlled by regulating both the rate of evacuation and rate of air admission.   The rate of flow should not be so great that the mass of material is splattered. Also the solid after sublimation may be so finely divided that collection is difficult.   Heating may be done by means of a bare flame, as for very high-boiling substances like 2-bromoanthraquinone, or by means of a liquid bath or a sand bath, as for easily sublimable solids.   A disadvantage of direct flame heating is possible decomposition, due to too high a temperature.

Chapter 12

DRYING

The process of drying solids has been discussed already in Chapter 5. There details are given for the removal of any liquid from the crystals. The term *drying*, as applied in this chapter to gases, means the removal of water vapor or the removal of any suspended liquid water such as spray or fog, and as applied to liquids, means the removal of dissolved water or of undissolved water in the form of visible drops or of an emulsion. The drying agents employed for removing water vapor from gases or dissolved water from liquids in general are effective also for removing undissolved water. Water is a contaminant in most preparations, owing to the fact that the reaction mixture or the product comes in contact with water at some time or other.

Drying may be accomplished by mechanical or chemical means. Water can be removed mechanically by distilling, freezing, filtering, or centrifuging, or chemically by a reaction with some substance. Suspended water in a gas, that is, a mist or fog, can be removed by filtering, or centrifuging, or by chemical means, and water vapor in a gas can be removed by freezing, or by chemical means. Suspended water in a liquid, that is, an emulsion, can be removed by any of the methods just mentioned, and water dissolved in a liquid usually can be removed by distilling or freezing, or by chemical means.

SECTION 12.1 DRYING BY MECHANICAL MEANS

12.11 Drying by Freezing. Often water can be removed from gases by cooling to $-75°$ with solid carbon dioxide, or to $-180°$ with liquid air. The water freezes out on the cooling surface. If the gas liquefies or if the substance to be dried is a liquid, separation from the ice may be accomplished by centrifuging in a cooled centrifuge or by filtering. Drying by cooling is not feasible if the substance solidifies.

Drying by freezing is possible so long as the vapor pressure of the water in the substance to be dried is above the vapor pressure of water over ice at the temperature of the cooling bath. Thus ice separates from the solution until the vapor pressure of water is the same above

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both phases. This is a very efficient means of drying, since at low temperatures the vapor pressure of ice is exceedingly low, and, hence, very little water is left in the substance to be dried. Table 12-1 shows the vapor pressure of ice at various temperatures.

TABLE 12-1

VAPOR PRESSURE OF ICE

Temp., °C.	V.P., mm. of Hg
−10°	1.95
−20°	0.78
−30°	0.29
−50°	0.030
−70°	0.0019
−80°	0.0004
−100°	0.0001

12.12 Drying by Distillation. A liquid may be dried by simple distillation with or without a fractionating column (Chapter 9). In the distillation of many liquids containing water, both the water and the liquid come over during the first part of the distillation as an azeotropic mixture. Naturally, as soon as all of the water has distilled over, the condenser and the upper part of the distilling apparatus should be dried before any attempt is made to collect the anhydrous product. A liquid boiling above 100° is more easily dried this way than one boiling below 100°.

If the azeotropic mixture is composed of two phases, as usually is the case if water and the liquid to be dried are not miscible, the two phases can be separated and redistilled separately to yield the dry material practically quantitatively, as pointed out in Subsection 9.23.

If the azeotropic mixture is cloudy, owing to a small amount of suspended water, this can be removed easily with a suitable chemical drying agent (see Section 12.2). Only a relatively small amount is necessary.

If water and the liquid to be dried form a single-phase azeotropic mixture, drying by distillation is possible only if the azeotropic mixture is richer in water than is the liquid to be dried. Thus, dry ethanol (absolute alcohol) may be obtained by fractionation at 760 mm. only from those water–alcohol mixtures that contain less than 4.4% water.

Drying of a single-phase azeotropic mixture, one component of which is water, may be accomplished by: (1) distilling at some other pressure, since the composition of azeotropic mixtures varies with the pressure (Section 9.3); (2) adding a third volatile liquid which is not miscible with water, and obtaining a three-component azeotropic mixture on

distillation. The added material should be one that can be removed by distillation. Thus, absolute alcohol is made by adding benzene to 95.6% ethanol, distilling over an azeotropic mixture of 16.9% alcohol, 74.5% benzene, and 8.5% water until all of the water has been removed, and then fractionating to remove remaining benzene as the azeotropic mixture of benzene and ethyl alcohol. Finally anhydrous alcohol is distilled. The ternary azeotropic mixture boils at 64.5°, and the binary at 68.2°.

The removal of water from a reaction mixture is effective in driving to completion a reversible reaction in which water is one of the products (see Chapter 1). This can be done by distillation, when water is part of a constant-boiling mixture. Thus, in Experiment 21–2, The Preparation of n-Butyl Acetate, water is removed as an azeotropic mixture of acetic acid, n-butyl alcohol, n-butyl acetate, and water. The distillate on cooling separates as two phases. The organic phase is returned to the reaction flask, and the water is discarded.

The distillation method is excellent for removing water from solids by first adding a liquid which either forms an azeotropic mixture with water or else boils above water. Then on distillation the water distils either as the azeotropic mixture or alone.

SECTION 12.2 DRYING BY CHEMICAL MEANS

There are two types of chemical drying agents, namely: (1) those that react irreversibly with water and (2) those that combine reversibly with water, by either hydrate formation or adsorption. In some instances the distinction is not a sharp one.

When water reacts irreversibly, the drying agent cannot be recovered from the reaction product. Thus, water reacts with phosphorus pentoxide to form phosphoric acid and with sodium metal to form sodium hydroxide and hydrogen gas. When water reacts reversibly, the original material usually can be recovered in anhydrous condition merely by heating the hydrated material to a sufficiently high temperature or by reducing the pressure of water vapor above it to a sufficiently low value. This is the case with salts that form hydrates, that is coordination compounds with water, and with many finely divided solids that strongly adsorb water.

12.21 Properties of Drying Agents. The properties a good chemical drying agent should possess are: (1) compatibility with the substance to be dried; (2) ability to dry intensely, that is, to remove water as completely as possible; (3) rapidity of absorption of water; (4) a high drying capacity; and (5) easy removability from the dried substance.

These factors seldom are of equal importance but may vary with the different materials being dried.

12.22 Compatibility of Drying Agent and Liquid to Be Dried. A drying agent should not be used if it reacts with the liquid to be dried, or if it catalyzes a reaction of the liquid. Thus, potassium carbonate, although good for drying many substances cannot be used for drying acids. And, likewise, acidic drying agents like phosphorus pentoxide cannot be used to dry basic substances. Often a drying agent absorbs a substance by forming a loose coordination complex with it. Thus, calcium chloride absorbs by complex formation many oxygen- or nitrogen-containing compounds such as the lower alcohols, esters, aldehydes, amines, and amides. Also care should be taken that the drying agent does not catalyze a reaction of the substance to be dried. For example, an aldehyde should not be dried with an acidic or basic drying agent since these catalyze polymerization. In Table 12–2 are listed some common drying agents.

TABLE 12–2

SOME COMMON DRYING AGENTS

$MgClO_4$ (Anhydrone) $BaClO_4$ (Desicchlora)	These are very powerful drying agents and may be regenerated by heating. They should not be used in the presence of acids since the liberated perchloric acid may form a powerful explosive mixture with organic matter. They may form explosive mixtures with various other organic compounds. These perchlorates usually are not available to beginning students since they are dangerous and relatively expensive.
$MgSO_4$ Na_2SO_4 $CaSO_4$ (Drierite) $CuSO_4$	These sulfates may be used for drying most substances, except that copper sulfate cannot be used with ammonia or amines. Copper sulfate and magnesium sulfate are satisfactory for most purposes in that they possess good intensity and good capacity. Sodium sulfate has low intensity and high capacity. Calcium sulfate has high intensity and low capacity.
$CaCl_2$	This forms complexes with many nitrogen- and oxygen-containing substances, especially amines and alcohols; however, it has good capacity and good intensity.
K_2CO_3	This may be used with all neutral or basic substances but cannot be used with acids.
KOH, NaOH CaO, BaO	These are excellent drying agents for basic or neutral substances but cannot be used for acids, esters, or aldehydes. Calcium oxide is satisfactory for alcohol.
P_2O_5 H_2SO_4	These are very powerful drying agents. They cannot be used for bases or unsaturated compounds or for many nitrogen- or oxygen-containing substances.

12.23   Drying by Hydrate Formation: Calcium Chloride as an Example. Calcium chloride forms hydrates containing four different amounts of water. These are stable at room temperature. They are the monohydrate $CaCl_2 \cdot H_2O$, the dihydrate $CaCl_2 \cdot 2H_2O$, the tetrahydrate $CaCl_2 \cdot 4H_2O$, and the hexahydrate $CaCl_2 \cdot 6H_2O$. The anhydrous salt and the different hydrates may all be used as drying agents, but they are not equally effective. This is evident from the following discussion on vapor pressure.
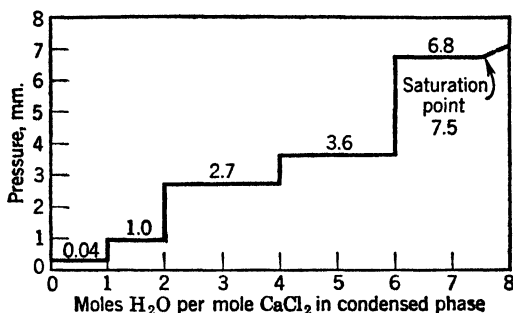
FIG. 12-1   Vapor-Pressure–Composition Diagram for the System, Water and Calcium Chloride, at 25°

In Figure 12–1 the pressure of water above the system as ordinates is plotted against the molar ratio of water to calcium chloride as abscissas.

When a substance containing water, that is, a liquid or a gas, is brought into contact with anhydrous calcium chloride, no hydrate forms unless the vapor pressure of water over the liquid or in the gas is greater than 0.04 mm., the vapor pressure of water over a mixture of calcium chloride monohydrate and anhydrous calcium chloride. If it is greater than 0.04 mm., water is absorbed by the anhydrous salt to increase the amount of the monohydrate and to decrease the vapor pressure of water in the liquid or in the gas until this reaches 0.04 mm., the value that is in equilibrium with the monohydrate and the anhydrous salt (it being assumed that the amount of calcium chloride is large enough). Thus, three substances are present after equilibrium is reached, namely, $CaCl_2$, $CaCl_2 \cdot H_2O$, and H_2O at a vapor pressure of 0.04 mm. The substance to be dried has no effect.

When anhydrous calcium chloride and its monohydrate are both present, the equilibrium vapor pressure of water has the constant value of 0.04 mm. at 25°, irrespective of the relative quantities of the two solid phases. This follows from the **phase rule,** which states that the

sum of the number of phases and the degrees of freedom in a system exceeds the number of components by two. Therefore, in this system of two components, calcium chloride and water, at a fixed temperature three phases can coexist at only one pressure. So long as any anhydrous salt is present, the equilibrium value does not rise above 0.04 mm.

If the amount of water in the system is sufficient to convert all the anhydrous calcium chloride present into the monohydrate and in addition to exert a vapor pressure greater than 1.0 mm., the minimum pressure exerted by the dihydrate, the monohydrate will absorb water from the substance until all of the monohydrate is converted into the dihydrate or until the vapor pressure of water is reduced to 1.0 mm., the equilibrium pressure of the system $CaCl_2 \cdot H_2O$, $CaCl_2 \cdot 2H_2O$, and H_2O vapor. Here again, according to the phase rule, three phases can coexist at only one pressure when the temperature is fixed.

If all of the monohydrate is converted to dihydrate and the pressure of water in the substance is still above 2.7 mm., the dihydrate will in turn absorb water until either it is converted completely to tetrahydrate or the pressure of water in the system drops to 2.7 mm. The absorption will continue in case the pressure remains above 3.6 mm. after all the dihydrate has disappeared, for then tetrahydrate will be converted into hexahydrate. If the pressure is still above 6.8 mm. after the tetrahydrate has been converted into hexahydrate, some of the latter will dissolve. The pressure of a saturated solution of calcium chloride at 25° is 6.8 mm. Finally, after all of the hexahydrate has dissolved, which requires 7.5 moles of water per mole of anhydrous calcium chloride, the aqueous solution will absorb water until its pressure of water vapor equals that in the system. From this it can be seen that the extent to which this absorption of water takes place depends in part on the initial vapor pressure of water in the system and in part on the molal ratio of water to calcium chloride.

From Figure 12–1 it is evident that the values for equilibrium pressures of water from the different "couples," or pairs of phases each having a definite vapor pressure, are 0.04, 1.0, 2.7, 3.6, and 6.8 mm., respectively. The first couple is the anhydrous salt and the monohydrate, the last is the hexahydrate and the saturated solution, and the other three are pairs of hydrates. Only after all of the hexahydrate dissolves can the pressure rise above 6.8 mm., since that is the vapor pressure of saturated calcium chloride solution at 25°, and the solution is saturated so long as any of the hexahydrate is present.

The final vapor pressure of water from a gas or liquid being dried is determined by the final state of the drying agent. If calcium chloride is present in two different phases, the final vapor pressure of water is

that of the particular couple. If the drying agent is present as one phase only, the vapor pressure of water in the system lies between the values for the two couples of which this phase can be a component. If no solid calcium chloride is present, the value will be above 6.8 mm.

Oftentimes equilibrium is not reached. The vapor pressure of water may be greater than that corresponding to the hydrates present, merely because of insufficient time and agitation. Or the surface of the anhydrous solid may be covered with a saturated solution of the hydrated form, owing to the fact that the lumps may be so large that time has not been sufficient for equilibrium to have been established between the anhydrous and hydrated forms.

12.24 Intensity of Drying and Selection of Drying Agent. The extent to which a liquid or gas may be dried by solids which like calcium chloride form solid hydrates is determined by the pressure of water vapor from the respective hydrates. These pressures may vary from the low value of 0.004 for $CaSO_4 \cdot 0.5H_2O$ to that of 19.2 mm. for $Na_2SO_4 \cdot 10H_2O$. The drying agents listed in Table 12–3 are in the approximate order of

TABLE 12–3

VAPOR PRESSURE OF WATER AT 25° ABOVE SOME DRYING COUPLES

Higher Hydrated Form	Vapor Pressure, Water, mm. Hg	Higher Hydrated Form	Vapor Pressure, Water, mm. Hg
$P_2O_5 \cdot H_2O(HPO_3)$	?	$KOH \cdot H_2O$	1.5
$BaO \cdot H_2O$ or $Ba(OH)_2$	10^{-16}	$KOH \cdot 2H_2O$	2
$Mg(ClO_4)_2 \cdot 3H_2O$	?	$ZnCl_2 \cdot 1.5H_2O$	2.3
$Ba(ClO_4)_2 \cdot 3H_2O$	?	$CuSO_4 \cdot H_2O$	0.8
$CaSO_4 \cdot 0.5H_2O$	0.004	$CuSO_4 \cdot 3H_2O$	4.7
$CaCl_2 \cdot H_2O$	0.04	$CuSO_4 \cdot 5H_2O$	7.8
$CaCl_2 \cdot 2H_2O$	1.0	$MgSO_4 \cdot H_2O$	1
$CaCl_2 \cdot 4H_2O$	2.7	$MgSO_4 \cdot 2H_2O$	2
$CaCl_2 \cdot 6H_2O$	3.6	$MgSO_4 \cdot 4H_2O$	4.9
$CaCl_2$ (sat. soln.)	6.8	$MgSO_4 \cdot 5H_2O$	8.8
$NaOH \cdot H_2O$	0.7	$MgSO_4 \cdot 6H_2O$	9.8
$CaO \cdot H_2O$ or $Ca(OH)_2$	0.8	$MgSO_4 \cdot 7H_2O$	11.5
$K_2CO_3 \cdot 1.5H_2O$	1.1	$Na_2CO_3 \cdot H_2O$	8.4
K_2CO_3 (sat. soln.)	9	$Na_2SO_4 \cdot 10H_2O$	19.2

their drying intensity. Naturally in the case of a substance like calcium chloride or magnesium sulfate, different intensities of drying can be realized, depending on the ratio of the amount of drying agent to the amount of water that must be removed. Sulfuric acid is an excellent drying agent. The vapor pressure of water from 95% sulfuric acid is

ca. 0.001 mm. and increases as water is absorbed. The vapor pressure is only 0.4 mm. from 75% sulfuric acid.

If water forms a perfect solution with the liquid to be dried, it will obey Raoult's law, and the vapor pressure of water will be proportional to its mole fraction. Thus, if the liquid were dried with sufficient anhydrous calcium chloride at 25°, the final vapor pressure of water would be 0.04 mm. (Table 12–3). The mole fraction of water in the liquid at equilibrium, N_{H_2O}, is

$$N_{H_2O} = 0.04/23.5$$

$$= 0.0017$$

since the vapor pressure of pure water at 25° is 23.5 mm. If the liquid had a molecular weight of 74, water would be present in a concentration of 0.042% by weight. If the hexahydrate-saturated solution were used, the mole fraction of water in the liquid would be 6.8/23.5 or 29 mole per cent, or about 9 weight per cent of the liquid after drying.

However, when water is not miscible or is only slightly soluble in the organic liquid, which is usually the case, the vapor pressure of water deviates quite widely from Raoult's law and exerts a much higher vapor pressure than calculated for an ideal solution. Therefore, drying is proportionately more intense than in the case just discussed. As an example, the vapor pressure of water at 25° from a saturated solution of water in *n*-butyl alcohol is about 22 mm., and the liquid is 50 mole per cent water (22 weight per cent) (see Figure 9–9). If it is assumed that in more dilute solutions of water in this alcohol the partial pressure of water follows Henry's law and drops off proportionally to the decrease in concentration, the alcohol after drying with the anhydrous calcium chloride–monohydrate couple would contain $0.5 \times 0.04/22$ or 0.09 mole per cent of water. Thus, the water remaining constitutes 0.023% by weight of the phases as compared to 0.042% for the ideal solution. If the hexahydrate-saturated solution couple were used, the water content would be about 4% by weight, compared with 9% for an ideal solution. In general, the lower the solubility of water in another liquid, the more intensely will a given drying couple dry it, and the smaller will be the amount of drying agent required.

From the information in Tables 12–2 and 12–3 and from a knowledge of the solubility of water in the liquid to be dried (in general, water is more soluble in those liquids that are more soluble in water), one can intelligently select the proper drying agent for the problem at hand. One must decide which reagent to select and how much of it to take. The intensity of drying desired, the amount of water to be removed, and

the removal of the drying agent must be given consideration. Since, in general, the system rarely comes to equilibrium, inasmuch as the time required for this to take place is seldom allowed, it is customary to use more drying agent than otherwise would be necessary. However, this entails more loss, as pointed out later under Removal of the Drying Agent, 12.28.

12.25 Effect of Temperature on Intensity of Drying. Lowering the temperature of a liquid increases the intensity of drying by means of a drying couple because of these effects: (1) The vapor pressure of water in equilibrium with the couple decreases logarithmically with temperature; (2) the solubility of water in organic liquids usually decreases as the temperature is lowered. Therefore, the drying agent should be removed from a liquid before the latter is distilled, since the drying agent will give up some water at the elevated temperature because of its higher vapor pressure, even though it was quite efficient at the lower temperature. However, if the partial vapor pressure of water from the drying couple is low at the temperature of distillation, the liquid may be distilled directly from the drying agent, as in Experiment 19–2, The Preparation of Absolute Alcohol.

12.26 Drying Capacity and Drying in Stages. It is best to use a drying agent that absorbs as large a quantity of water as possible, so that a minimum quantity of the substance to be dried will be left behind on the solid. Inspection of Table 12–3 shows how the various solids differ in their absorbing capacity.

When a large amount of water is to be removed, usually it is not desirable to try to obtain intense drying in one step, by the addition of a large amount of drying agent, because this entails excessive loss by entrainment of substance being dried. Preferably drying should be done in stages, especially if the drying agent forms more than one hydrate, by adding the drying agent in several small portions and removing each portion before adding the next. In this way the first portion of drying agent absorbs a relatively large amount of water through the formation of a higher hydrate or even of the saturated aqueous solution, but the drying will be less intense than that achieved by later portions which need remove relatively less water and thus may exert the drying power of the lowest hydrate.

12.27 Speed of Drying. Since drying is a heterogeneous chemical reaction, the factors that influence the rate of this type of reaction are operative here (see Chapter 1). These are mainly concerned with contact between the phases and are agitation, fineness of subdivision, and nature of the surface. A long period of standing with occasional shaking may take the place of vigorous agitation over a shorter period of time.

For this a wide-bottom flask, as for example an Erlenmeyer flask, rather than a test tube or a separatory funnel, should be used.

A disadvantage of a fine powder is its tendency to settle to the bottom. This may be overcome in part by the use of porous lumps. The latter has the advantage of ease of removal. However, both have the disadvantage of entraining much liquid. This is discussed more extensively under Removal of the Drying Agent.

12.28 Removal of Drying Agent. The dried liquid may be separated from the drying agent by: (1) decanting, (2) centrifuging, (3) filtering, or (4) distilling. The important precaution to take is avoidance of needless loss of liquid, which results from contact with the drying agent and with the necessary apparatus. The loss can be minimized by: (1) diluting the liquid with a suitable solvent, (2) washing the drying agent with a suitable anhydrous solvent, (3) cutting down the volume of the drying agent by using one of high capacity and/or by drying in stages, (4) using the drying agent in a form having a small surface, that is, granules rather than powder, or fused material rather than porous.

The precautions to be observed in mechanical separations by decanting, centrifuging, and filtering are much the same. Decanting is possible if the drying agent leaves a clear solution as it often does when it is in lump form. Generally, a finely powdered solid does not settle well, and for this reason some drying agents, for example calcium chloride, come in the form of lumps. However, if the amount of drying agent added is small, so that the "couple" is the hydrated form and the saturated solution, the drying agent may be added in the form of a finely divided solid. The mixture of solid and saturated solution is a pasty mass which settles out, leaving a clear liquid which may be poured off from the paste with minimum loss of substance. Care must be taken that droplets of saturated solution do not float on the surface. If these are observed, shaking must be continued until they join the rest.

Centrifuging is preferable to filtering, for it allows the liquid to be decanted after the solid has been forced into a small compact mass at the bottom of the centrifuge tube, especially when the solid is finely divided.

Filtering may be done through a small loose plug of absorbent cotton in the funnel stem rather than through filter paper, for the solid usually is comparatively coarse and is held on the cotton. The loss due to absorption by the filtering medium is thus diminished. But if the drying agent is finely divided, filtering through paper may be necessary.

Distillation has one advantage over the other methods in that a better recovery of the liquid being dried can be realized. As an example, in the preparation of absolute alcohol by refluxing with quick lime (Experi-

ment 19–2) decanting, centrifuging, and filtering are quite inefficient because the drying agent becomes finely divided and voluminous. On the other hand, distillation is an effective method of recovering the product. But, in general, distillation has the disadvantage that the drying agent, if it hydrates reversibly, exerts a higher vapor pressure of water, the higher the temperature. Therefore, the higher the temperature of distillation, the greater is the percentage of water in the distillate. Distillation is more adaptable to liquids that boil at, or close to, room temperature. If, however, the drying agent possesses a high intensity of drying, distillation from the residual solid may be satisfactory, as in Experiment 19–2, The Preparation of Absolute Alcohol.

Loss of material is diminished by diluting the liquid with a suitable solvent or by washing the drying agent with a suitable anhydrous solvent, for then the surface of the solid after separation is wet by a dilute solution of the solvent, rather than by the pure substance. The solvent should be one in which water is essentially insoluble and one that can be separated from the substance by distillation. The disadvantage of such a procedure is the necessity of removing the solvent by distillation.

The method of drying in stages has already been described (12.26). The operation is simplified if the drying agent forms a saturated aqueous solution with the water removed, for then this solution can be drawn off in a separatory funnel without loss of liquid being dried. Only those solids with a high solubility in water are satisfactory for this purpose, as for example potassium hydroxide, potassium carbonate, and calcium chloride. Then less solid is necessary for drying the remaining liquid, thus cutting down loss by entrainment. The technique is illustrated in the use of potassium carbonate. The finely divided solid should be added in small portions and the mixture shaken vigorously for several minutes. Then the aqueous phase that develops is drawn off before more solid is added. This is repeated until a thick paste results. Since this adheres firmly to the glass, the liquid, usually clear, can be poured out at the top of the separatory funnel.

The advantage of minimizing loss of material through decreasing the surface of the drying agent is counterbalanced by lowered speed of drying (12.27).

12.29 Relative Costs. An expensive drying agent should not be used when a cheaper one will do the work. The most expensive drying agents are phosphorus pentoxide, anhydrous magnesium perchlorate (anhydrone), and anhydrous barium perchlorate (desicchlora). The cheapest are sulfuric acid, technical quick lime, and technical (flake) caustic soda and caustic potash. Next cheapest are anhydrous sodium sulfate, potassium carbonate, and calcium chloride.

Chapter 13

ALKANES; PARAFFIN HYDROCARBONS

Alkanes may be prepared by certain general methods: (a) the decarboxylation of fatty acids by heating the sodium salts with soda lime, (b) the electrolysis of the sodium or potassium salts of the fatty acids, (c) the decomposition of Grignard reagents by water or alcohol, (d) hydrogenation of alkenes, (e) the reaction of sodium with alkyl halides (Wurtz synthesis):

(a) $$CH_3COONa + NaOH \rightarrow CH_4 + Na_2CO_3$$

(b) $$CH_3COO^- - E^- \rightarrow [CH_3COO]$$

$$2[CH_3COO] \rightarrow CH_3CH_3 + 2CO_2$$

(c) $$C_2H_5I + Mg \rightarrow C_2H_5MgI$$

$$C_2H_5MgI + H_2O \rightarrow C_2H_6 + IMgOH$$

(d) $$C_5H_{11}CH{=}CH_2 + H_2 \rightarrow C_5H_{11}CH_2{-}CH_3$$

(e) $$2C_2H_5I + 2Na \rightarrow C_2H_5{-}C_2H_5 + 2NaI$$
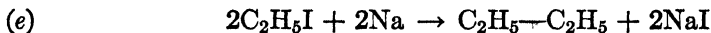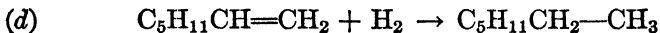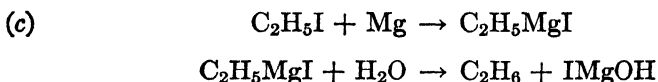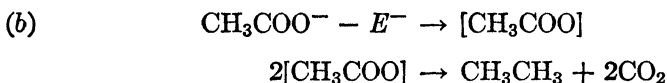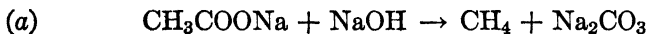
The hydrocarbon prepared has by method a one less carbon atom in the molecule than has the original compound, by method b two less than twice the original number, by methods c and d the same number, and by method e twice the original number of carbon atoms. The hydrocarbons prepared by methods c and d usually are quite pure; the purity of the products by the other methods is less and in general decreases in the order: e, b, and a.

13.11 Decarboxylation of Salts of Acids. In method a rather extensive side reactions take place, except in the case of sodium acetate. Unsaturated hydrocarbons also are formed. Even methane prepared by this method contains impurities. The reaction is not very complete since reactants and one product are solids.

13.12 Electrolysis of Salts of Fatty Acids. In method b the yields are low.

13.13 Hydrolysis (or Alcoholysis) of the Grignard Reagent. In method c the hydrocarbon is generated by adding water (or alcohol) to the ether solution of the Grignard reagent (Chapter 18). Usually

the reaction is so rapid that, in those cases where the hydrocarbon is a gas, excessive spurting takes place. The reaction may be controlled by using a dilute solution of water (or alcohol) in a suitable solvent, for example ether. The yield usually is good.

13.14   Hydrogenation of Alkenes.   In method d reaction takes place readily at atmospheric pressure in the presence of a suitable catalyst such as specially prepared platinum, palladium, or nickel. The reduction can be made to take place in the pure liquid or in a solution of dioxane or alcohol. The reaction proceeds much more rapidly when hydrogen at a higher pressure is used, or when the reaction temperature is raised.

13.15   The Wurtz Synthesis.   Method e has the advantage of yielding a fairly pure product when the reaction is carried out with a single alkyl halide. When two halides are present, three products are possible. For example, if ethyl iodide CH_3CH_2I, and n-propyl iodide $CH_3CH_2CH_2I$, are used, n-butane $CH_3CH_2CH_2CH_3$, n-pentane $CH_3CH_2CH_2CH_2CH_3$, and n-hexane $CH_3CH_2CH_2CH_2CH_2CH_3$ are formed. The proportions in which these are formed depend on the relative concentrations and reactivities of the halides. The reaction is slow since the system is heterogeneous, and the sodium becomes covered with a layer of sodium halide. The reaction can be aided by application of the principles discussed in Chapter 1. This reaction is discussed more completely in Chapter 29 as the Wurtz–Fittig reaction in the aromatic series.

The alkyl halides should be so selected that they do not boil near the desired hydrocarbon. Thus in some cases, iodides may be preferred; in others, bromides. Likewise, any solvent should be properly selected.

Experiment 13–1   Preparation and Properties of Methane

A   PREPARATION OF METHANE.   Grind to a powder and mix intimately (Note 1) in a mortar 10 g. of *freshly fused* sodium acetate (Note 2) and 10 g. of soda lime.   Transfer the mixture to a 20-cm. test tube provided with a rubber stopper fitted with a delivery tube.   Support the tube by means of a clamp with the open end slightly lower than the closed end.   Connect with apparatus for collecting the gas over water.   Calculate the volume of methane with which 250 cc. of air will unite completely (assuming that air contains one fifth its volume of oxygen), and place this volume of water in a 250-ml. bottle.   Heat the tube carefully with a luminous fishtail flame.   Ignite test-tube portions from time to time, and discard the product until the burning proceeds slowly for several seconds.   Collect three 250-ml. bottles of the gas.   Finally displace with methane the water added to the fourth bottle, taking care that gas does not enter after the water is displaced.

B   COMBUSTION OF METHANE.   Apply a lighted match to one bottle of the gas.   In order to facilitate the removal of the gas, a stream of water should be poured into the bottle while the gas is burning.   Describe what happens.

Drop a lighted match into the bottle containing the mixture of methane and air.   Compare the result with that obtained with the other sample.

C   BROMINATION OF METHANE.   Add 2 to 3 drops of bromine from a dropper to one bottle of the gas (Note 3).   Cover with a glass plate, and allow to stand, preferably in the sunlight, until the reaction is complete.

D   BROMINATION OF LIQUID HYDROCARBONS.   Determine the action of bromine and of iodine on ordinary kerosene and on kerosene purified by shaking with fuming sulfuric acid.

Notes

1. Chemical action between solids is seldom as complete as between liquids, or between solids and liquids (see 1.15).

2. Sodium acetate is available as the anhydrous and hydrated forms, CH_3COONa and $CH_3COONa \cdot 3H_2O$.   The anhydrous form readily absorbs moisture from the air and on this account should be dehydrated by fusion just before use.   To dehydrate, place in an iron dish, *securely fastened*, as for example on a support stand between two iron rings, and heat with a bare flame.   The hydrated form melts in its water of crystallization, and, as the water is driven off, a light fluffy solid is left.   As the heating is continued, the anhydrous solid fuses to a dark liquid which on cooling solidifies to a hard cake.   Heating, if continued beyond this stage, causes decomposition.   Stirring while cooling serves to break up the large lumps.

3. Bromine vapor will ruin the rubber nipple if allowed to remain in contact with it.

Questions

1. What are the equations for the reactions in A, B, and C?

2. Why is not chemical action between solids usually complete?

3. How can you tell when the action between bromine and methane is complete?

4. Is there evidence of the formation of reaction products in C and D?

5. How may methane be obtained from methyl iodide?

6. Summarize the general methods for preparing the paraffin hydrocarbons.

7. Write equations for any other chemical reactions that methane undergoes.

8. Do you consider methane to be a reactive substance chemically? Explain.

9. What is kerosene? Is it a reactive substance chemically?

10. From free-energy data calculate the equilibrium constant for the hydrogenation of ethylene.

11. Calculate the heat of reaction of ethyl iodide with metallic sodium.

12. Write the balanced chemical equation for the preparation of ethane from acetate ion.

13. If ethyl iodide and n-propyl iodide are equally reactive with respect to the Wurtz reaction, what would be the theoretical yields of n-butane, n-pentane, and n-hexane, starting with 1 mole of each iodide?

Chapter 14

ALKENES; OLEFINS

Alkenes are produced in large quantities industrially by the cracking of petroleum products, and usually as complex mixtures in which are present paraffins and dienes (diolefins) as well as alkenes. The preparation of olefins in the laboratory may be realized by (a) the dehydration of alcohols, (b) the dehydrohalogenation of alkyl halides (preferably bromides or iodides) by heating with a base, (c) the dehalogenation of olefin dibromides by the action of metallic zinc, (d) the reaction of Grignard reagents with allyl bromide, (e) the reaction of metallic zinc with β-bromoethers (Boord synthesis):

(a) $CH_3CHOHCH_3 \rightarrow CH_3CH{=}CH_2 + H_2O$

(b) $CH_3CHBrCH_3 + KOH \rightarrow CH_3CH{=}CH_2 + KBr + H_2O$

(c) $CH_3CHBrCH_2Br + Zn \rightarrow CH_3CH{=}CH_2 + ZnBr_2$

(d) $C_2H_5MgBr + BrCH_2CH{=}CH_2 \rightarrow C_2H_5CH_2CH{=}CH_2 + MgBr_2$

(e) $CH_3OCH(CH_3)CH_2Br + Zn \rightarrow CH_3CH{=}CH_2 + BrZnOCH_3$

Method a serves for the preparation of some olefins in a reasonably pure state, for example ethylene, propylene, isobutylene, 2-butene, and 2-pentene. Method b yields an essentially pure olefin if the alkyl halide is symmetrical or if it is a primary halide. Methods c, d, and e yield essentially pure hydrocarbons.

14.11 Dehydration of Alcohols. Method a is followed in Experiments 14–1, 14–2, and 14–3. This method is discussed in detail later.

14.12 Dehydrohalogenation of Alkyl Halides. In method b, reaction may be carried out by heating the alkyl halide with sodium or potassium hydroxide, either in the solid state or in a suitable solvent, that is, one that dissolves both the base and the organic halide. Use of alkali in the solid state has the disadvantage that the base soon becomes covered with alkali halide. When a solvent is present, the temperature is limited by the boiling point of the solution. For this reason a high-boiling solvent is preferable, in order to obtain a higher rate. Among the solvents that can be used are: ethyl alcohol C_2H_5OH; dihydroxy-

diethyl ether or "diethyleneglycol," $O(CH_2CH_2OH)_2$; its monoethyl ether or "carbitol" $HOCH_2CH_2OCH_2CH_2OC_2H_5$; and its monobutyl ether or "butyl carbitol" $HOCH_2CH_2OCH_2CH_2OC_4H_9$.

A side reaction is the formation of ether. This is the main reaction between primary halides and lower alcohols:

$$CH_3CH_2CH_2CH_2Br + HOC_2H_5 + KOH \rightarrow$$

$$CH_3CH_2CH_2CH_2OC_2H_5 + KBr + H_2O$$

14.13 Dehalogenation of Olefin Bromides. Method c is of value in the purification of olefins, since the dibromide, which can be prepared by direct union of bromine with the olefin, usually can be purified by distillation or crystallization. The debromination reaction takes place readily on heating an alcoholic solution of the dibromide with metallic zinc, as in Experiment 14–4. Alcohol is added for the purpose of controlling the reaction rate by keeping the concentration of the dibromide low and by keeping the temperature from rising above the boiling point of alcohol. Also it dissolves zinc bromide. Potassium iodide or magnesium metal may be used in place of zinc.

14.14 Reaction of Grignard Reagents with Allyl Bromide. Method d is a general synthetic method for 1-alkenes (α-olefins). Ethylmagnesium bromide may be replaced by some other Grignard reagent. Homologs of allyl bromide are not satisfactory, owing to a side reaction; for example, crotyl bromide $CH_3CH\!=\!CHCH_2Br$ yields with ethylmagnesium bromide two products, namely, 2-hexene $C_2H_5CH_2$-$CH\!=\!CHCH_3$ and 3-methyl-1-pentene $C_2H_5CH(CH_3)CH\!=\!CH_2$. In Chapter 18 is a more detailed discussion of the preparation and application of the Grignard reagent.

14.15 The Boord Synthesis. Method e is valuable for the preparation of higher olefins. In the following equations, which show the steps, R represents an aliphatic radical, C_nH_{2n+1}:

$$CH_3CHO + HCl + CH_3OH \rightarrow CH_3CHClOCH_3 + H_2O$$

$$CH_3CHClOCH_3 + Br_2 \rightarrow BrCH_2CHBrOCH_3 + HCl$$

$$BrCH_2CHBrOCH_3 + RMgBr \rightarrow BrCH_2CHROCH_3 + MgBr_2$$

$$BrCH_2CHROCH_3 + Zn \rightarrow CH_2\!=\!CHR + BrZnOCH_3$$
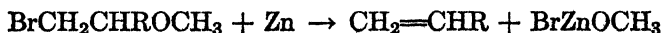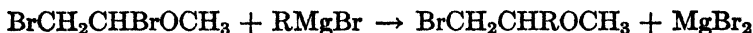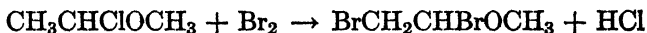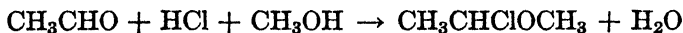
The first step is the formation of an α-chlorinated ether from aldehyde, anhydrous hydrogen chloride, and methanol; the second step is the conversion of this chlorinated ether to an α,β–dibromoether through bromination; the third step is the reaction of this with a Grignard reagent with replacement of the α-bromine atom by the alkyl radical; the fourth step

is the decomposition of the resulting product with zinc. The reaction is extended by the use of higher aldehydes. The first three reactions must be carried out rapidly and with especial care, because α-halogenated ethers are unstable.

14.16   Thermochemistry.   For reactions a, b, and c, approximate values of ΔH are listed in Table 14–1.   In the cases of b and c the re-

TABLE 14–1

APPROXIMATE ENERGY CHANGES IN FORMATION OF A GASEOUS OLEFIN

	Reaction	ΔH from Bond Energies, kcal.	ΔH from Heats of Formation	ΔH of Over-all Reaction
a	$CH_3CHOHCH_3(g) \rightarrow CH_3CH=CH_2(g) + H_2O(g)$	$+5.7$ *		$+5.7$
b, 1	$CH_3CHBrCH_3(g) \rightarrow CH_3CH=CH_2(g) + HBr(g)$	$+12.6$		
b, 2	$HBr(g) + KOH(s) \rightarrow KBr(s) + H_2O(l)$		-51.7	-39.1
c, 1	$CH_3CHBrCH_2Br(g) \rightarrow CH_3CH=CH_2(g) + Br_2(g)$	$+20.5$		
c, 2	$Br_2(g) + Zn(s) \rightarrow ZnBr_2(s)$		-85.6	-65

* From Equation 1–25, Chapter 1.

actions are considered to take place in two steps, for convenience in calculation.   In this way the advantages of making use of bond energies can be retained.   For the first step the energy change is calculated from bond energies and for the second, involving only inorganic compounds, from heats of formation.

From Table 14–1 it is evident that reaction a is endothermic, and reactions b and c are strongly exothermic. Reaction d likewise is exothermic. It would be expected, from Section 1.4, that reactions b, c, and d would proceed well to completion towards the right. Reaction a must be discussed in more detail.

The heat change in the gaseous dehydration of ethyl alcohol to ethylene can be calculated accurately, since the heats of combustion are accurately known.

$$CH_3CH_2OH(g) \rightarrow CH_2=CH_2(g) + H_2O(g)$$
$$336.7 337.3 9.5 \quad \Delta H = +10.1 \text{ kcal.}$$
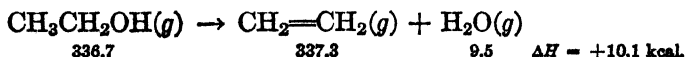
Here 336.7 and 337.3 kcal. are the molal heats of combustion of gaseous alcohol and ethylene, respectively, and 9.5 kcal. is the heat of vaporization of water.   The values of $+5.7$ kcal. from bond energies, and of $+9.6$ kcal., from equilibrium measurements at higher temperatures in the range, 300° to 400°, are in satisfactory agreement with $+10.1$ kcal. above.   Since the products differ in number from the reactants, and since the numerical value of ΔH is below 15 kcal. (refer to Subsection

1.43) an approximate value for ΔF and thus for the equilibrium constant cannot be obtained from ΔH.

The value of ΔF calculated from the free energies of formation of the compounds involved is $+1.91$ kcal. per mole (Equation 1–33) and leads to a value of 0.04 for the equilibrium constant. Thus, if reaction could take place at room temperature, the equilibrium would lie well on the side of the alcohol. Actually no reaction takes place in either direction, and no catalyst is known that promotes reaction at 25°. At temperatures high enough to cause reaction to take place in the absence of a catalyst, side reactions may become significant. Thus, a catalyst must be present and the temperature must be raised before a reaction involving ethyl alcohol, ethylene, and water will take place. Another effect of increasing the temperature is a shift in the position of equilibrium (Subsection 1.32), and this favors dehydration at the higher temperature more than at the lower temperature.

14.165 Catalysis. For the gas-phase dehydration of ethyl alcohol at temperatures near 350°, many solids can be used, of which aluminum oxide, thorium oxide, and anhydrous aluminum sulfate are the most effective. These are typical gas-phase **dehydration catalysts.** The product is a mixture of alcohol, ethylene, and water, from which alcohol and water are condensed by cooling.

For the liquid-phase dehydration of alcohols and the hydration of olefins, strong proton donors are the best catalysts. Aside from perchloric acid, which cannot be used since it reacts explosively when heated with alcohols, sulfuric acid is the strongest proton donor. The effect of sulfuric acid is essentially catalytic and is not due to heat of combination with the water formed. The heat of addition of sulfuric acid and water, an effect that would favor the dehydration reaction, is largely counteracted by the heat of addition of sulfuric acid with alcohol, an effect that would favor the hydration reaction. The effectiveness of an acid is increased by decreasing the water–acid ratio, and the alcohol–acid ratio. Thus, the presence of any water in the sulfuric acid diminishes the catalytic effect, because the proton activity has been lowered, since hydronium ion H_3O^+ is a much weaker proton donor than concentrated sulfuric acid. Also the presence of water or alcohol reduces the boiling temperature of the mixture. The effect of dilution is evident from this: alcohol when heated with concentrated sulfuric acid at 150° yields ethylene, but the reaction does not proceed if the sulfuric acid previously has been diluted with one half its weight of water.

The acid-catalyzed reaction is promoted by many insoluble siliceous materials, for example kieselguhr, Fuller's earth, diatomaceous earth, or powdered pumice. Anhydrous aluminum sulfate prepared by cal-

cining ammonium alum, also is useful. Hyflo diatomaceous earth is one of the best.

Alcohols of different types do not decompose with the same ease; tertiary alcohols react most readily; primary least. This is brought out in Table 14-2, which shows the experimental conditions prevailing in the preparation of some olefins.

TABLE 14-2

EXPERIMENTAL CONDITIONS IN THE PREPARATION OF SOME OLEFINS

Olefin	Alcohol Used	H_2SO_4, wt. %	Moles H_2SO_4, per Mole Alcohol	Approximate Temperature, °C.
Ethylene	Ethanol	concd.	1.8-2	140-150
Propylene	1-Propanol	75	2.5-3	100-150
Propylene	2-Propanol	65-70	2-2.5	60-120
2-Butene	1-Butanol	70-75	2.5-3	120-160
2-Butene	2-Butanol	60-70	2-2.5	70-140
2-Pentene	sec-Amyl alcohol	60	2-2.5	60-110
Isobutylene	tert-Butyl alcohol	20 *	1	86-96
Cyclohexene †	Cyclohexanol	65-70	1-2	105-115

* Or oxalic acid.
† Taken off through a fractionating column.

The differences noted in the table become understandable when the thermochemistry of the *tert*-butyl alcohol–isobutylene equilibrium is considered. In this case ΔH of dehydration in dilute aqueous solution is +12.8, and ΔF is +1.33 kcal. Moreover, the reverse rate, that of hydration of the olefin, is so fast at room temperature that in 1 M sulfuric acid about half the olefin reacts within 15 minutes. Since the equilibrium does not lie so far on the alcohol side as in the case of ethyl alcohol, it is evident that the dehydration reaction has a measurable rate under these conditions. Moreover, since ΔH for the dehydration of tertiary butyl alcohol is larger than that of ethyl alcohol, a rise in temperature causes a more rapid change in the equilibrium constant, thus aiding the dehydration. Therefore, at the boiling point of tertiary butyl alcohol, the equilibrium which is set up fairly rapidly between the alcohol and the hydrocarbon in the presence of the catalyst is disturbed by the continual removal of the gaseous olefin, while the alcohol is returned to the reaction flask by means of a reflux condenser. There is no evidence indicating the formation of butyl hydrogen sulfate. The actual intermediate is an oxonium ion of the type $C_4H_9OH_2{}^+$.

The dehydration of the secondary alcohols, 2-butanol and 2-pentanol, is similar thermodynamically to that of *tert*-butyl alcohol except that with the former the rates are lower and the equilibria probably lie further on the alcohol side. Therefore, the catalyst must be more effective (less water present), and the temperature must be higher. The secondary alcohols thus lie between ethanol and the tertiary alcohols in the ease of dehydration. Primary alcohols of larger molecular weight are more easily decomposed than ethanol (compare with 1-butanol).

In the gas-phase dehydration of ethanol over solid catalysts the temperature must be carried higher than in the liquid acid-catalyzed dehydration, partly because such catalysts probably are not so effective as concentrated sulfuric acid, and partly because the reverse reaction is prominent, owing to the fact that both the reaction products are present.

When 1-butanol is decomposed over an aluminum oxide catalyst, the product is mainly 1-butene, with smaller amounts of *cis*- and *trans*-2-butene. When the catalyst is sulfuric acid, the product is a mixture of *cis*- and *trans*-2-butene, but none of the expected 1-butene.

14.17 Side Reactions. Polymerization is the side reaction which may accompany any of these dehydrations if the strength of the acid (acid–water ratio) is too great. For the lower olefins the relative tendencies to polymerize are: ethylene < propylene < normal butylenes < isobutylene. Of the reactions shown in the table, polymerization is most troublesome in the case of 75% sulfuric acid and 1-butanol. Since branched-chain olefins having the isobutylene structure polymerize with ease, the use of acid much stronger than the one indicated is not advisable. Apparently little polymerization takes place in the ethylene preparation, even though the acid concentration is high. The polymerization reaction is diminished by dilution.

Ether formation may accompany any dehydration, because this reaction also is catalyzed by acids (see Chapter 22). Oxidation of the alcohol by the sulfuric acid is possible when the acid is concentrated, as in the preparation of ethylene. However, sulfuric acid of the concentration corresponding to the dihydrate, $H_2SO_4 \cdot 2H_2O$ has little or no oxidizing action.

14.18 Purification and Recovery of a Liquid Olefin. A liquid olefin usually is purified by distillation. Distillation usually is satisfactory for removing the alcohol, which constitutes the principal impurity, for it has a much higher-boiling point than the olefin. Polymers also have higher-boiling points.

If the olefin is passed through a fractionating column as it leaves the reaction mixture, the purification thereby effected renders subsequent purification easier. Of course, the kind of column depends on the

properties of the compounds involved. A complication is the possibility that polymerization may be more extensive, since the olefin remains in contact with the acid for a longer period of time.

14.185 Purification and Recovery of a Gaseous Olefin. A gaseous olefin, as for example ethylene, propylene, or butylene, may be purified by passing through suitable scrubbers to remove gaseous impurities, of which the most important is the alcohol itself, and sometimes sulfur dioxide, from reduction of the sulfuric acid. If this is condensed with the olefin, as for example with 2-butene (Experiment 14–2), a white polymer forms. This is composed of both olefin and sulfur dioxide. Special pains must be taken to be sure that the apparatus does not leak. The olefin is either converted to the olefin bromide or condensed to a liquid by means of a suitable low-temperature bath. Storage in the form of the dibromide is preferred if the olefin tends to polymerize, or if there is likelihood that the vessel may break as a result of excessive pressure. The olefin can be recovered from the dibromide by the action of metallic zinc, method *c*.
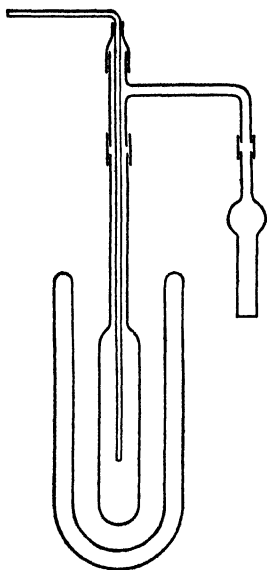
FIG. 14–1 Ampoule for Collecting a Condensable Gas

For collecting a condensed gaseous olefin the apparatus of Figure 14–1 is recommended. The condensation is done in an ampoule, which can be made easily from glass tubing, 20 to 30 mm. in diameter, by closing one end and sealing onto the other end a piece of smaller tubing, 7 to 8 mm. in diameter and 200 to 300 mm. long. The main section is 100 to 150 mm long and should have a capacity about twice the expected volume of the liquid, in case the cooling bath is −80° or lower, to allow for expansion of the liquid on warming to room temperature. A T tube is attached by a piece of rubber tubing to the open end of the stem, so that the ends touch. A long narrow tube, for conducting the gas into the ampoule, extends through the T tube to the middle of the ampoule and is connected to the top of the T tube by an air-tight rubber connection. The tube should not extend below the expected liquid level; otherwise, the liquid may suck back if the pressure drops. A guard tube containing anhydrous calcium chloride is attached to the side arm of the T tube, to prevent entrance of moisture. The cooling bath may consist of ice and salt, or ice and concentrated hydrochloric acid, or solid carbon dioxide and isopropyl ether. Dry Ice is a

more effective condensing agent than any freezing mixture made with ice, since it cools to a lower temperature. However, frequent replenishment is necessary. The bath should have sufficient capacity and should be insulated. When Dry Ice is the cooling agent, the container should be a Dewar jar. The cooling bath should be deep enough to submerge the main section of the ampoule and a part of the narrow tube above it.

In sealing the ampoule, some precautions are necessary. The ampoule should be surrounded by an efficient cooling bath. The interval of time between disconnecting the ampoule and the sealing operation should be as short as possible to minimize contamination with moisture. After the ampoule is disconnected, vapor of olefin in the stem should be removed by *gentle* suction through a narrow tube, to prevent pyrolysis while sealing. Sealing should be done by means of a blast lamp, preferably with a horizontal flame. First a tube or rod is attached to the end of the stem, and then the tube is sealed as close to the end as possible, the attached tube being used as a handle. In this way the flame can be kept away from the bath, and only a small length of the stem is lost.

14.19 Reaction of Olefins with Chlorine and Bromine. This type of reaction is discussed in Chapter 17, which should be read if an olefin halide is being prepared, as in Experiment 14–1. One should note that ethylene gas has a low solubility in liquid bromine at room temperature. This is one factor that tends to retard the reaction. The principles discussed in Chapter 1 should be applied, if a faster reaction is desired (refer especially to 1.15).

Experiment 14–1   Preparation of Ethylene and Ethylene Bromide

Set up the following apparatus, connected in series: (1) a 1-liter distilling flask (Note 1) supported by a clamp 1 to 2 cm. above a burner and fitted with a cork stopper carrying a thermometer and a safety tube which extends about 50 cm. above the top of the stopper, both reaching nearly to the bottom of the flask (Note 2); (2) three bottles provided with inlet and outlet tubes, the inlet tubes extending nearly to the bottom (Note 3); (3) a fourth bottle, loosely connected, with an inlet tube extending only about half way down. The third bottle, which may be replaced by a test tube, is placed in a vessel through which water circulates (Note 4) and is so connected that it can be shaken easily. Use cork stoppers throughout, as an exercise in cork boring. (However, see Note 1; refer to Experiment 3–1, Note 4.) Be sure that each vessel is air-tight before starting on the next. The apparatus must be air-tight and must be approved by the instructor before you proceed. If you have not done so already, collect pertinent data in the form of a table before proceeding (see page 2).

Place in the flask, disconnected for the purpose, 1 mole of 95 or 96% ethyl alcohol (Note 5). Add slowly with shaking 1.8 to 2 moles of concentrated sulfuric acid, and *mix thoroughly* (Note 6). Then add 4 to 5 g. of siliceous material (see discussion). Put concentrated sulfuric acid in the first bottle, aqueous sodium hydroxide (about 6 N) in the second (both one-third to one-half full), 0.25 mole of bromine (Note 7; *Caution:* Note 8; weigh or measure carefully *under the hood* and make all transfers there) in the third, and aqueous sodium hydroxide in the fourth to within about 1 cm. of the inlet tube. Do not connect the bromine bottle until most of the air is expelled from the apparatus by the ethylene.

Heat the flask until the thermometer registers 140–150°. At this temperature evolution of gas should be fairly rapid. If it is not, the temperature may be carried a few degrees higher. As soon as the air is largely expelled from the apparatus, slacken the flow; attach the bromine bottle, and continue the flow of gas at such a rate that the ethylene largely reacts with bromine (Note 9). A decomposition temperature of 145–160° is usually satisfactory; if it is higher than this, charring becomes troublesome. If the mixture chars badly, it probably will be necessary to replace it with a new charge. Before emptying the flask, dilute the contents with much water. Pour it into the hood sink, and wash it down with a good stream of water. Try to identify by odor an inorganic compound often present in the reaction mixture.

The reaction between ethylene and bromine takes place slowly, partly on account of the low solubility of ethylene in bromine, the short period of contact, and the negative catalytic effect of excess bromine. The reaction can be accelerated by illumination or by raising the temperature. (Refer to Subsection 1.15 for methods of increasing rates in heterogeneous systems.) Continue until the color of bromine disappears.

Shake the liquid in a separatory funnel two or three times with water to remove most of the acid present, using two separatory funnels for convenience (refer to 6.17). Remove any halogen and all remaining acid with dilute aqueous sodium carbonate (refer to 6.13 and 6.16), and wash finally with water to remove sodium carbonate. Shake the organic phase with a small amount of suitable drying agent (potassium carbonate or calcium chloride) so as to dry in stages (refer to 12.26), removing the aqueous phase and repeating. In case the liquid must stand for a time, run it into a small conical flask, and add a little more of the drying agent. Let stand until water is well removed (refer to 12.26). Remove the drying agent by proper filtration (refer to 12.28) into a dry distilling flask of suitable size (refer to 7.11) attached to a small dry water-cooled condenser.

Distil slowly with a *small* flame, so as to distil over completely at the beginning any water remaining, thus completely drying the main portion

of the product (refer to 12.12).   Collect separately in a small flask the first, cloudy distillate.   Stop when the distilling temperature is constant and/or water no longer comes over.   Remove water from the distillate and also from the cooler part of the distilling apparatus where it has condensed.   Add the dried liquid to the boiler.

Continue with the distillation, and collect in a small weighed flask the portion that distils in a 5° range near the boiling point of ethylene bromide.   Determine the melting point.   Calculate the percentage yield from both bromine and alcohol taken (Note 10).

Label the flask with name of substance, weight, corrected melting and boiling points, percentage yield, and name of worker.   Complete the write-up and report to the instructor.

Notes

1. A three-necked reaction flask may replace the distilling flask.   This has the advantage that the safety tube may be attached at one neck, a thermometer for recording the temperature of the reaction mixture at a second, and a reflux condenser (refer to 7.23) or a fractionating column at the third neck.   These two serve to minimize loss of alcohol.   Fitting such a flask and refluxing apparatus with cork stoppers usually provides sufficient exercise in cork boring.   The rest of the train can then be put together with rubber connections.

2. The safety tube should turn over at the top so as to drain into a flask, in case of stoppage.   A U bend at the bottom diminishes loss of gas but is not important.

3. Because gas easily leaks through improperly fitted cork stoppers, special care must be taken in preparing and boring such stoppers (see Experiment 3–1, Note 4) and in fitting the glass tubes, which must not have sharp edges.   Short pieces of rubber tubing are permissible for holding together glass tubes.   Long pieces of rubber tubing should be avoided.   The apparatus must be neat looking and air-tight and must be approved by the instructor.   Be sure you know how to bore a stopper satisfactorily by getting one connection air-tight before going on to the next.   Note that in a 250-ml. bottle the bromine is only about 5 mm. deep.

4. The purpose of the water bath is to keep the bromine from vaporizing, rather than to lower the reaction rate.   If a test tube is used, due allowance must be made for the volume increase by calculation from densities.   In case the ethylene seems to react slowly, refer to 1.15.

5. To prepare propylene and propylene bromide, the excess of alcohol over the 0.25 mole of bromine need be only about 100%.   The reason is that propylene reacts more rapidly than ethylene.   In place of concentrated sulfuric acid, which causes polymerization of propylene when heated, add the correct amount of sulfuric acid (see Table 14–2) in the form of a cold or warm (not hot) diluted acid of the correct strength (*Caution:* see Experiment 14–2, Note 3).   When the alcohol is 1-propanol (*n*-propyl alcohol) the acid should be about 75%, and, when it is 2-propanol (*sec*-propyl alcohol; isopropyl alcohol), the acid should be about 65%.   Check calculations with the instructor.

In case the total volume of liquid is too small, or if the evolution of propylene ceases before all the alcohol has decomposed, add more sulfuric acid of the proper

strength. Sometimes, especially when refluxing is inadequate, a 100% excess of alcohol is insufficient.

The sulfuric acid in the wash bottles should be 40 to 50% (*Caution:* see Experiment 14–2, Note 3), since propylene is absorbed by 65% or stronger acid.

6. Thorough mixing is difficult to accomplish while the flask is attached to the apparatus. If the mixing is not thorough, the acid in the bottom of the flask is not sufficiently diluted with alcohol. By the time the temperature reaches 150°, extensive charring will take place. *Caution:* Concentrated sulfuric acid is corrosive. Any that is spilled should be diluted at once with water and at once neutralized with aqueous sodium bicarbonate.

7. If desired, some water may be added. However, the surface area between liquid bromine and gaseous ethylene is then less.

8. *Caution:* Don't breathe bromine vapor. In case liquid bromine comes in contact with the skin, immediately wash the skin with water, alcohol, or acetone and then with aqueous sodium bicarbonate.

9. Bromine vapor is carried out of the bottle by any unreacted ethylene.

10. The yield from bromine is 80%.

Questions

1. What are the functions of the safety tube?

2. What can be used instead of the sulfuric acid in the generating flask?

3. Explain carefully the purpose of the first, second, and fourth bottles.

4. What modifications of the apparatus would be advantageous?

5. Why is there no advantage in a very rapid flow of gas?

6. Discuss losses, aside from the mechanical losses involved in handling the product.

7. What size distilling flask did you use? Why this size?

8. Why not leave the drying agent in the liquid during the final distillation?

9. How may ethylene be prepared from the ethylene dibromide?

10. Is a catalyst needed in the preparation of ethylene from ethyl alcohol?

11. If a very much more effective catalyst could be found, would you expect to be able to obtain ethylene from alcohol at 25°?

12. Is there any objection to carrying the reaction temperature much above 150°?

13. How are olefins produced on a large scale?

14. What substances add readily to olefins?

15. Calculate ΔH for the formation of ethylene bromide from ethylene and bromine.

16. What impurity or impurities are present in the final product and to what extent? (Refer to Table 4–1.)

17. State the steps which have been taken to remove them.

Experiment 14–2   Preparation of 2-Butene

Provide a 500-ml. three-necked reaction flask (Note 1) with: (1) a glass safety tube about 4 feet high leading nearly to the bottom of the flask and bending at the upper end so as to drain into another flask of 500-ml. capacity (Note 2); (2) a reflux condenser (refer to 7–23); and (3) a ther-

mometer for recording the temperature of the reaction mixture. To the upper end of the condenser attach glass tubing which leads to the purifying train below. The bottom of the reaction flask should be about 2 cm. above the burner. Make the necessary connections above with cork stoppers, as an exercise in cork boring (refer to Experiment 3–1, Note 4). Test each stopper for air tightness as it is bored, rather than wait until all are bored. Often, otherwise, it is necessary to rebore the entire lot. Therefore, be sure you can get one connection air-tight before proceeding to the next. The apparatus must be air-tight and must be approved by the instructor before you proceed. If you have not already done so, collect pertinent data in the form of a table before proceeding (see page 2).

For purifying the butene, construct apparatus of four wash bottles (*ca.* 250 ml.) and a drying tower not less than 15 cm. high, making connections with rubber if desired (note that some rubber tubing is somewhat permeable to butene; refer to Experiment 14–1, Note 3). Place 50 to 55% sulfuric acid (Note 3) in the first two bottles, aqueous sodium hydroxide (3 to 6 N) in the last two bottles, soda lime in the first half of the drying tower, and anhydrous calcium chloride in the second half (Note 4).

For collecting the butene, construct apparatus of an ampoule (see Figure 14–1 and discussion, especially that on Recovery of a Gaseous Olefin), a T tube, a calcium chloride guard tube and a vertical glass tube 20 to 25 cm. long, long enough to extend well into the body of the ampoule and small enough to slip through the T tube and the neck of the ampoule. Connect this tube to the tower outlet. The lower end of the ampoule should be at least 1 foot above the table top so that a cooling bath can be dropped down and moved away easily. By suitable-sized rubber tubing make connections to the T tube as follows: at the top, the narrow vertical tube mentioned previously; at the bottom, the collecting ampoule; at the side, the guard tube (Note 5). Make all connections air-tight. Report to the instructor, for testing. *Weigh the ampoule* before starting the experiment. Enter the weight in your notebook.

In the generating flask, disconnected, add with agitation and cooling under the tap about 2.5 moles of concentrated sulfuric acid to the correct amount of water to give an acid of 65 to 70% sulfuric acid by weight (Notes 3 and 6). Mix *thoroughly*, and cool to below 60°. Then add 1.0 mole of anhydrous 2-butanol (Notes 7 and 8) and 2 to 4 g. of siliceous material (see discussion), and again mix thoroughly. Connect the apparatus, and immerse the ampoule in a cooling bath. The bath should be in a Thermos (or Dewar) jar *ca.* 20 cm. long in case Dry Ice is the

cooling agent, or in a tall jar of 8- or 10-liter capacity if a freezing mixture is the cooling agent (refer to discussion).

Heat the generating flask with a flame. A gas will be evolved as the temperature rises. Regulate the rate of flow by the heating, so as to complete the reaction in about 1 hour. The bath temperature should not rise above −10°. In case the evolution of gas is slow, add more concentrated acid (20 to 30 g.) with agitation, but only after the reaction mixture has been cooled. *Caution:* Mix *thoroughly* before heating. Continue until gas is no longer evolved.

Disconnect the ampoule, and, while it is still in the cooling bath, seal it in the flame of a blast burner (Note 9). Weigh the sealed tube and the small piece of glass drawn off, obtaining the weight of 2-butene by difference. Calculate the percentage yield (Note 10). Label the product showing name, weight in grams, percentage yield, date, and temperature of the liquid when the ampoule was sealed (Note 11). Complete the write-up, and report to the instructor.

Notes

1. If a three-necked flask is not available, use a 500-ml. round-bottomed flask, and attach to it a two-necked addition tube so constructed that the safety tube can pass out one neck and the condenser can be attached to the other. The thermometer can be dispensed with.

2. This collects the reaction mixture in case of stoppage. A U bend at the lower end of the safety tube decreases loss of butene through the tube but is not necessary.

3. *Caution:* Concentrated sulfuric acid is corrosive. Any sulfuric acid spilled on hands, clothing, desks, or floor should be diluted at once with water and at once neutralized with aqueous sodium bicarbonate. When diluting sulfuric acid, add the acid to water, *mixing thoroughly*, preferably by swirling while cooling the flask under the tap. The 50 to 55% acid for the wash bottles is approximately 40% sulfuric acid by volume. It absorbs vapors of butyl alcohol but little or no butene. It may be made up approximately. The acid for the reaction mixtures should be of a known strength, and for this purpose it is necessary to determine the strength of the concentrated sulfuric acid before diluting it. Check calculations with the instructor before proceeding.

4. Stoppage occurs if water remains in the butene. A medium or large drying tower is necessary.

5. Uncondensed butene can be detected by attaching a bubbling device to the guard tube. A wide U tube, with just enough liquid to form a seal, is safe since liquid will not be drawn into the apparatus.

6. Refer to Table 14–2. With 60% acid the rate of evolution of butene is low, but polymerization is negligible.

7. Sometimes 2-butanol contains water, for it may be marketed in the form of the azeotropic mixture (see Table 16–1). When the alcohol is shaken with a small amount of potassium carbonate, the solid should not become mushlike, or liquefy.

8. 2-Butanol may be replaced by 1-butanol. Here also the reaction product is 2-butene, which is essentially a similar mixture of *cis-* and *trans-2*-butene. In this

case a larger volume of acid may be taken, to diminish side reactions. The sulfuric acid must be more concentrated (Table 14–2), and the temperature required is higher. The yield is 65%. The extent of the side reactions is greater in this case. The butene from 1-butanol may in some instances be the purer, for the only other alcoholic contaminant is a trace of ethyl alcohol, if the butanol is prepared by the butyl alcohol fermentation process (Commercial Solvents Corp.). On the other hand 2-butanol may contain some 2-propanol, 2-pentanol, or 2-methyl-2-propanol.

9. *Caution:* The flame of the burner should not come close to the freezing bath, for the ether may ignite. It is not necessary to seal the tube if the butene can be kept cold until needed, as, for example, in the preparation of 2,3-dibromobutane (Experiment 17–1) or of 3-chloro-2-butanol (Experiment 19–5).

10. Yield is 75 to 85%.

11. It is important to indicate the temperature at which the ampoule was sealed since it should be cooled to this temperature before opening.

Questions

1. What are the functions of the safety tube?
2. What is the purpose of the sodium hydroxide wash bottle?
3. Why not use concentrated sulfuric in the first and second wash bottles instead of the 50% acid?
4. Can 2-butene be kept in a glass-stoppered bottle? Explain.
5. How else may 2-butene be prepared? Write equations.
6. Is there evidence that any other reaction has taken place? Explain.
7. How could this reaction be minimized without decreasing the rate of evolution of butene?
8. What products might 1-butanol be expected to yield on dehydration? Ditto, 2-butanol?
9. Why does a large amount of acid serve to diminish side reactions?
10. Explain why 2-butanol is liable to be contaminated with other alcohols.
11. Is a catalyst necessary in the dehydration of 1-butanol or 2-butanol?
12. Is a catalyst used here?
13. Compare the weights of ice and Dry Ice theoretically required to condense 1 mole of butene in this experiment. State the assumptions made and what excess is desirable.
14. Why should the ampoule, before being opened, be cooled to the temperature at which it was sealed?
15. How many structurally isomeric butenes, formula C_4H_8, are possible? How many, including stereoisomers?
16. What impurity or impurities are present in the crude and final products and to what extent?
17. State the steps that have been taken to remove them.

Experiment 14–3   Preparation of 2-Pentene (Note 1)

Set up a distilling apparatus according to Figure 7–1, using a 500-ml. distilling flask and a long condenser (jacket *ca.* 90 cm. long). Replace the guard tube with a piece of rubber tubing which extends outside a window or almost to the floor (Note 2). If you have not already done so, collect pertinent data in the form of a table before proceeding (see page 2).

Dilute about 2 moles of concentrated sulfuric acid to 60 or 65% by weight by adding it, with agitation in a suitable flask while cooling under the tap, to the correct amount of water (Note 3). Add 1.0 mole of anhydrous secondary amyl alcohol (Note 4) and 2 to 4 g. of some siliceous material (see discussion) to the cold diluted acid, mix *thoroughly*, and transfer the mixture to the distilling flask. Heat on a steam or hot-water bath to obtain a slow distillation of 2-pentene, keeping the distilling temperature reasonably close to that of the pure hydrocarbon (Note 5). Continue as long as pentene distils. This requires 2 to 3 hours.

Without removing the pentene from the receiver, agitate it well (Note 6) with about 25 ml. of ice-cold 1 or 2 N sodium hydroxide. Add some cold water, pour the mixture into a separatory funnel, and draw off the aqueous phase (Note 7). Add a small amount of a suitable drying agent (refer to 12.22 and 12.26), and agitate gently but long enough to remove water. Transfer the pentene (refer to 12.28) to a suitable dry distilling flask (refer to 7.11). With a *very* small flame (Note 8) distil over the pentene, collecting a 5° fraction near the boiling point of 2-pentene, in a previously weighed flask or sample bottle (Note 9). If the distillate is cloudy, continue the distillation until the liquid drops off clear, thus drying the main portion by distillation (see 12.12). Recombine, after drying the wet distillate with a small amount of drying agent, and continue.

Label the product showing name, boiling range, weight in grams, percentage yield, date, and name of student; complete the write-up of the experiment and report to the instructor.

Notes

1. *Caution:* Pentene is very volatile, the vapor is easily ignited, and mixtures of pentene vapor and air are explosive. Be sure that all connections are air-tight, and take care to keep flames away from the exit tube.

2. By this arrangement the vapor of pentene is kept away from the flames on the desk.

3. *Caution:* Refer to Experiment 14–2, Note 3.

4. This is a mixture of 2-pentanol and 3-pentanol.

5. By noting the temperature of distillation one can tell if the distillate contains much secondary amyl alcohol.

6. *Caution:* Pressure is developed when the pentene is shaken in a closed vessel (see Experiment 6–1).

7. If an emulsion develops, refer to Subsection 6.16, Emulsions. In case addition of acid is desirable, add some ice first, to keep cool.

8. By removing the barrel tube of a Tirrill gas burner, a fine jet flame can be obtained at the base.

9. In case the residue in the boiler is significant in amount, continue the distillation until its volume is small, making cuts at appropriate temperatures. Redistil in systematic fashion (refer to 9.13).

10. Yield is 75%. The yield is 80% from 2 moles of alcohol.

Questions

1. Excluding cyclic compounds, how many structurally isomeric pentenes, formula C_5H_{10}, are possible? How many, including stereoisomers?

2. Show by means of structural formulas the difference between 2-pentanol and 3-pentanol.

3. What products might each be expected to yield on dehydration?

4. What is the source of commercial secondary amyl alcohol?

5. What is the purpose of shaking with aqueous sodium hydroxide?

6. Why does pressure develop when pentene is shaken in a closed vessel?

7. Is a catalyst necessary in the dehydration of secondary amyl alcohol?

8. Is any catalyst used here?

9. What impurity or impurities are present in the crude and final products and to what extent?

10. State the steps that have been taken to remove them.

11. Explain how the boiling temperature is lowered by the presence of moisture.

Experiment 14–4   Preparation of a Gaseous Alkene from the Dibromide

Properties of Alkenes

A   Preparation.   Place in a large test tube or a suitable flask 10 ml. of an olefin bromide (Note 1), 10 ml. of alcohol, and 4 g. of sheet zinc, the latter cut into pieces so small that the liquid completely covers it. Attach a delivery tube, for collecting the gas in 250-ml. bottles, over water. Warm the mixture, and, as soon as a sample of the gas collected in a test tube burns quietly when ignited, fill three bottles. Finally, just displace from a fourth bottle an amount of water equivalent to the theoretical volume of the alkene that will combine with the air in the bottle (Note 2).

B   Combustion.   Apply a lighted match to one bottle of the gas. Pour water into the bottle as the gas burns, in order to facilitate the removal of the gas. Compare the results with methane (or natural gas).

Apply a match to the mixture of the alkene and air. ·

C   Oxidation by Permanganate.   Add a few drops of potassium permanganate solution to another bottle of the gas, replace the cover, and shake.

Repeat the test with illuminating gas, collected in the same way.

Add one drop of 2-pentene to a few milliliters of permanganate solution (Note 3).

D   Addition of Bromine.   Add about one fourth of the theoretical amount of bromine from a dropper to the remaining bottle.   Place in the sunlight for a few minutes.   Remove any bromine remaining by the addition of aqueous sodium hydroxide.   Compare with the action of bromine and a paraffin hydrocarbon.

Add pentene drop by drop to about 5 ml. of a solution of bromine in carbon tetrachloride.   Note if hydrogen bromide is evolved (Note 4).

Add a drop of a solution of bromine in carbon tetrachloride at the same time to small samples of (a) ordinary kerosene; (b) the same, previously purified by shaking with concentrated sulfuric acid.   Note any differences in rate of disappearance of color or evolution of hydrogen bromide

Notes

1. This procedure is satisfactory for the preparation of ethylene, propylene, or a butylene from the corresponding dibromide.   For obtaining a liquid alkene from its dibromide, a reflux condenser is attached to the reaction vessel (a flask may be used) and the mixture refluxed until all of the dibromide has reacted.   The desired alkene may be separated from most of the alcohol by distillation.   A butene can be obtained as a liquid by condensing with Dry Ice, using the apparatus described in Experiment 14-3.

A liquid olefin can be tested for flammability, and also for reactivity with permanganate and bromine.   However, for the test with bromine only a small volume should be taken.

2. Show in your laboratory notes how you calculate this volume.

3. This is the Baeyer test for unsaturation.   It is characterized by rapid reduction of neutral permanganate, even when cold.

4. Rapid decolorization without significant formation of hydrogen bromide is a characteristic reaction of olefi

Questions

1. What are the equations for the reactions in A, B, C, and D?
2. Is there any evidence of a chemical change in D?
3. Of what value is the Baeyer test?
4. What conclusion do you draw from the test of illuminating gas with potassium permanganate?
5. What do you conclude to be the effect of treating kerosene with sulfuric acid?
6. What is ΔH of the reaction of an alkene dibromide with zinc?
7. What is ΔH of the reaction of an alkene with bromine?
8. What statement can you make in regard to the reversibility of this reaction?

Chapter 15

ALKYNES

Alkynes may be prepared conveniently by: (*a*) alkylation of acetylene or of a monalkylated acetylene by the action of an alkylating agent (alkyl halide or alkyl sulfate) with the sodium salt; (*b*) dehydrohalogenation of a suitable haloalkene or dihaloalkane with potassium hydroxide; (*c*) dehydrohalogenation with sodamide.

(*a*) $$HC\equiv CH + Na \rightarrow HC\equiv CNa + \tfrac{1}{2}H_2$$

$$HC\equiv CH + NaNH_2 \rightarrow HC\equiv CNa + NH_3$$

$$CH_3(CH_2)_3Br + NaC\equiv CH \rightarrow CH_3(CH_2)_3C\equiv CH + NaBr$$

$$CH_3(CH_2)_3C\equiv CH + Na \rightarrow CH_3(CH_2)_3C\equiv CNa + \tfrac{1}{2}H_2$$

$$CH_3(CH_2)_3C\equiv CNa + H_2O \rightarrow CH_3(CH_2)_3C\equiv CH + NaOH$$

$$CH_3(CH_2)_3C\equiv CNa + C_4H_9Br \rightarrow$$

$$CH_3(CH_2)_3C\equiv C(CH_2)_3CH_3 + NaBr$$

(*b*) $$CH_3CH_2CH_2CHBrCH_2Br + KOH \rightarrow$$

$$CH_3CH_2CH_2CH=CHBr + KBr + H_2O$$

$$CH_3CH_2CH_2CH_2CHBr_2 + KOH \rightarrow$$

$$CH_3CH_2CH_2CH=CHBr + KBr + H_2O$$

$$CH_3CH_2CH_2CH=CHBr + KOH \rightarrow$$

$$CH_3CH_2CH_2C\equiv CH + KBr + H_2O$$

(*c*) $$CH_3CH_2CH_2CHBrCH_2Br + 3NaNH_2 \rightarrow$$

$$CH_3CH_2CH_2C\equiv CNa + 2NaBr + 3NH_3$$

$$CH_3CH_2CHBrCHBrCH_3 + 3NaNH_2 \rightarrow$$

$$CH_3CH_2CH_2C\equiv CNa + 2NaBr + 3NH_3$$

$$CH_3CH_2CH_2C\equiv CNa + HOH \rightarrow CH_3CH_2CH_2C\equiv CH + NaOH$$

Method a is a general synthetic method for the preparation of monoalkyl and dialkyl acetylenes and usually yields pure products. All the normal alkynes from 3 to 11 carbon atoms have been synthesized this way. Method b often yields a mixture of an alkadiene and alkyne. Method c yields pure 1-alkynes.

15.11 Alkylation of Alkynes. In method a sodium acetylide is prepared by running a solution of metallic sodium in liquid ammonia into a solution of acetylene in liquid ammonia. This is much better than passing acetylene into a solution of sodium in liquid ammonia, because the solubility of acetylene is greatly depressed by dissolved sodium. A suspension of sodamide in liquid ammonia may replace the solution of metallic sodium. The alkyl halide is added slowly, and the reaction proceeds smoothly at the boiling point of ammonia (Experiment 15–1). The monosubstituted acetylene, 1-hexyne in the case previously cited when 1-bromobutane is used, may be converted into the sodium salt by reaction with more sodium or sodamide. Sodium has the disadvantage that some of the alkyne is reduced to the corresponding alkene. A disubstituted acetylene, in this case 5-decyne, can be obtained by a repetition of the process. Dry Ice is used as a cooling agent. A reflux condenser (Figure 7–2) cooled by Dry Ice prevents loss of ammonia and allows the reaction mixture to stay at the boiling temperature. Moisture should be excluded.

15.12 Dehydrohalogenation with Potassium Hydroxide. In method b the splitting out of the elements of hydrohalic acid to produce a double bond or a triple bond can be accomplished by heating with a strong base, for example potassium hydroxide. Potassium hydroxide may be either in the form of a finely divided solid or dissolved in a suitable solvent, which also dissolves the organic halogen compound (see discussion on dehydrohalogenation, Chapter 14).

The reaction takes place in two steps. The first step is the formation of a haloalkene. This undergoes dehydrohalogenation more slowly, and also it boils at a much lower temperature than the dihalide does. When a solvent is used, the dihalo compound should be added slowly to the hot solution of potassium hydroxide, and the reaction products should be passed through an efficient fractionating column. In this way the haloalkene is returned to the reaction flask, and the alkyne distils over. Also, the reaction temperature and therefore the rate is lowered if a large amount of haloalkene is allowed to accumulate, which is the case if the dihalide is added too rapidly. Bromine compounds have the advantages over chlorine compounds that they are more reactive and boil at higher temperatures.

15.13　Dehydrohalogenation with Sodamide. Method c, which is especially useful in the preparation of 1-alkynes, is carried out by refluxing the halogen compound with a suspension of sodamide in high-boiling ligroin. This is prepared by carefully adding the ligroin to liquid ammonia containing sodamide and allowing the ammonia to evaporate. Sodamide accomplishes dehydrohalogenation more effectively than does potassium hydroxide, since it is a stronger base. Any 1-alkyne is converted to the sodium alkynide. Also, any 1,3-alkadiene or 2-alkyne is converted to the same sodium alkynide, merely by heating with excess sodamide for some time. Rearrangement takes place slowly. Any unconverted haloalkene, alkyne, or alkadiene is expelled by distillation before the sodium alkynide is decomposed by adding water.

Method c is especially useful for converting the following into 1-alkynes:

1. Olefins, through the olefin dihalides.
2. Ketones and aldehydes, through the corresponding α,α-dihalogen compounds, which result by treatment with phosphorus halides.

15.14　Thermochemistry. In method a data are not available for calculating ΔH for the reaction between sodium acetylide and an alkyl bromide. However, like other reactions of alkyl bromides with salts of weak acids, it probably is exothermic. In methods b and c the important ΔH values to consider are those associated with the second step, in which the trebly bonded compound is formed from the doubly bonded compound. For the first step, ΔH in method b is approximately that associated with alkene formation, as listed in Table 14–1 (but slightly more negative, as a result of resonance in halides of the vinyl type). In order to make use of bond energies, as in Chapter 14, the formation of the alkyne from the bromoalkene is considered to take place in two steps. The values so obtained, shown in Table 15–1, probably differ

TABLE 15–1

APPROXIMATE ΔH VALUES IN DEHYDROBROMINATION OF A GASEOUS BROMOALKENE

Reaction	ΔH, from Bond Energies, kcal.	ΔH, from Heats of Formation, kcal.	ΔH of Over-all Reaction, kcal.
$b, 1$　$CH_2{=}CHBr(g) \rightarrow CH{\equiv}CH(g) + HBr(g)$	$+23$		
$b, 2$　$HBr(g) + KOH(s) \rightarrow KBr(s) + H_2O(l)$		-52	-29
$c, 1$　$CH_2{=}CHBr(g) \rightarrow CH{\equiv}CH(g) + HBr(g)$	$+23$		
$c, 2$　$HBr(g) + NaNH_2(s) \rightarrow NaBr(s) + NH_3(g)$		-57	-34

somewhat from experimental values, since heats of solution have been disregarded.

It is evident from Table 15–1 that both reactions are so strongly exothermic that the reactions would be expected to proceed well towards completion. However, comparison with Table 14–1 shows that the change is less than when an olefin is prepared. This shows that a triple bond is not formed so easily as a double bond.

15.15 Rates. Reactions of method *a* take place at the boiling point of liquid ammonia. In methods *b* and *c* heating is necessary. The heterogeneous nature of the system in method *c* necessitates vigorous agitation.

15.16 Side Reactions. In method *a* some dialkylacetylene is formed, since some sodium salt of the monoalkylacetylene is present in the reaction mixture. This is due to the distribution of the sodium between acetylene and the monoalkylacetylene. In case metallic sodium is used, some of the alkyne undergoes reduction. In method *b* diene formation may be important.

15.17 Sealed Mechanical Stirrers. A simple seal is obtained by extending under the surface of the liquid the bearing tube in which the shaft of the stirrer rotates. This type of seal usually is not very efficient, because the surface of the liquid may drop below the end of the tube, especially if the stirring is vigorous or if the liquid is not deep enough. Another simple type of seal consists of a rubber connection extending just far enough beyond the end of the bearing tube to enclose the shaft of the stirrer. The connection must be loose enough to allow the shaft to rotate freely. Either or both ends of the bearing tube may be so equipped. Another type of seal is the mercury-sealed stirrer, shown in Figure 15–1.

Experiment 15–1   General Method of Preparing 1-Alkynes

1-Hexyne

Equip a 2-liter two-necked flask (Note 1) with a Dry Ice reflux condenser of good capacity (Note 2) and a wide inlet tube extending about half way down, for introducing ammonia. Be sure no moisture is present. Make all connections air-tight, so that condensed moisture cannot leak through (Note 3). To the outlet tube of the condenser attach a guard tube of soda lime or of solid caustic in flake or pellet form (Note 4). To the inlet tube attach dry rubber tubing, to connect with a tank of anhydrous ammonia.

Have available also a 3-liter four-necked flask (Note 5) equipped with a sealed mechanical stirrer (Note 6; see discussion) and so constructed that the reflux condenser can be transferred later, if desired,

with a minimum of effort.   Provide also a connection between the flasks, to be used later for slow transference of sodium solution.   This is made of wide glass tubing (O.D. not less than 8 mm., Note 7) which leads from the bottom of the 2-liter flask to the upper third of the 3-liter flask, and well to the center so that liquid will drop on to actively moving material.

Also make provision to run a stream of purified acetylene into the second flask and well to the bottom.   Take acetylene from a cylinder or tank and pass it through two wash bottles of con-
centrated sulfuric acid (Note 8).   Connections to the
flask must be air-tight.

For direct cooling of the flasks, particularly the 3-liter flask, in a bath of Dry Ice and a suitable solvent (Note 2), provide a crock of about 2-gallon capacity, for then the operations of collecting the liquid ammonia and running in acetylene can be shortened.   Preferably the crock should be set on a stand so that, by moving the stand to one side, the crock can be dropped and moved to one side.   This permits change without altering adjustments, as for example exchange of flasks.   Have available at least two guard tubes (Note 4), so that at no time will moisture from the air be drawn into either flask.   Set up the apparatus in a well-ventilated hood, but do not start the experiment until a continuous period of about 6 hours' time is available.   Collect pertinent data in the form of a table (see page 2).

FIG. 15–1   Mercury-sealed Stirrer

SODIUM ACETYLIDE.   After the Dry Ice condenser is charged (Note 2), collect liquid ammonia, either by allowing gaseous ammonia to enter the flask as rapidly as the condenser can condense it, or preferably run in liquid ammonia by placing the tank in the proper position and open-
ing the valve wide (Note 9).   Keep the condenser charged with Dry Ice, and collect about 1 liter of liquid ammonia.   Remove the inlet tube, and attach a tightly fitted guard tube (Note 4) in case the reflux condenser is dispensed with.   Have outlet to air through a glass tube, which later, with attached rubber tube, can serve as a pressure regulator.

From a larger piece of metallic sodium trim off any crust (*Caution:* Note 10), and cut off a piece about 1.3 g. at. wt. of sodium.   Without delay, cut this into a number of pieces that will enter the flask easily (Note 11), and place them under kerosene for temporary storage.   Add the sodium to the ammonia a piece at a time, after quickly absorbing

most of the kerosene with paper. Do not leave the flask open any longer than necessary. Add 1.3 g. at. wt. of sodium. Solution of the sodium usually is complete after about ¼ hour. Presence of solid sodium can be detected with a stirring rod. It is not advisable to swirl the liquid, for rapid boiling may cause liquid to spurt out of the flask.

While the sodium is dissolving, collect about 1.5 liters of liquid ammonia in the 3-liter flask as before. From this point on, immerse the flask in the −80° bath, if one is available. Attach stirrer and acetylene inlet tube. The condenser can be dispensed with here if the flask is cooled by the −80° bath, but there must be an outlet to air, properly protected. Saturate with acetylene gas. Then connect the two flasks so that the sodium solution can be forced over into the second flask. Close the exit to air on the first flask with rubber tubing and screw clamp. Regulate the flow of liquid by adjusting the clamp.

Run the blue ammonia solution of metallic sodium into the acetylene solution only as rapidly as the blue color is discharged, while stirring continuously and passing in a stream of acetylene. In case the acetylene solution becomes blue, stop the flow of liquid (Note 12), and build up an excess of acetylene before continuing. Sodium acetylide separates as a white solid. Before all the solution has been transferred, add more liquid ammonia, to replace evaporation losses. After all the solution has been transferred, remove the cooling bath so that the temperature will rise to the boiling temperature of liquid ammonia. The reflux condenser can be attached at one neck (see Note 2).

1-HEXYNE. While stirring, allow 1.0 mole of n-butyl bromide (Note 13) to flow slowly into the flask, under control (note that boiling increases). Stir for at least 2 hours at the boiling point. To recover any hexyne from escaping ammonia during these operations, attach to the guard tube, by air-tight connections, a suitable absorbing train. This must have good capacity and not allow water to be drawn into the flask (Note 14).

Add under control 100 to 150 ml. of redistilled dibutyl ether (Notes 15 and 16) to collect the product, and then, also under control but as rapidly as feasible, 100 to 200 ml. of pure water so as to eliminate any unreacted sodium, sodamide, or sodium acetylide and to dissolve sodium compounds. Stir all the time, but note that violent stirring is liable to cause troublesome emulsification (refer to 6.16). Let ammonia evaporate through a tube, so as to prevent easy access of air. Preferably allow to evaporate slowly, although cautious heating is possible (Note 17). In case the phases do not separate well, add more water. Separate in a separatory funnel, taking precautions against excess pressure (refer

to 6.17). In case any hexyne was collected in the absorbing vessel, run the ether solution into the flask, and then separate the aqueous phase.

Shake the organic phase a few times with water and then with dilute hydrochloric acid (2 or 3 N) until all ammonia is removed (refer to Section 6.1). Repeat a few times with water, and then dry with a suitable drying agent (refer to Section 12.2). If the liquid must stand for some time, transfer it to a small conical flask with some of the drying agent. When ready to distil, remove the drying agent by proper filtration (refer to 12.28) into a flask from which distillation is to be made. This should be dry.

Distil out the hexyne from the solvent in dry apparatus through an efficient packed fractionating column (refer to 9.14 and 9.15). Collect separately in a small flask any fraction coming over below the boiling point of the desired product. If this is cloudy, continue until clear, in this way removing water and thus drying the main portion of the liquid by distillation (refer to 12.12). Dry this distillate with a small amount of drying agent, remove any condensed water from the cooler portions of the apparatus (including condenser), add the dried liquid to the main portion, and continue with the distillation. Collect a clear distillate in a 5° range near the boiling point of the expected product (Note 18). Handling is minimized if the product is collected directly into a weighed ampoule which can be sealed to prevent absorption of oxygen. Continue the distillation until the distilling temperature approximates that of dibutyl ether, making cuts at intervals of 10° or 20°. In case the intermediate fractions are substantial, refractionate slowly (refer to 9.13) in smaller apparatus (refer to 9.15).

From the weight of the product calculate the percentage yield, based on the alkyl bromide. If the product is collected in a flask, transfer it without undue delay to an ampoule for sealing off. Label properly with name, boiling point, weight in grams, percentage yield, and name of worker. Complete the write-up and report to the instructor (Note 19).

Notes

1. Select the 2-liter and 3-liter flasks so that the Dry Ice reflux condenser can be fitted to either one.

2. Outside cooling by Dry Ice is recommended. This may be done by attaching a suitable reflux condenser and/or by immersing the flask in a cold liquid bath. The reflux condenser (Figure 7-2, I) preferably should hold about 750 ml. of liquid, especially if ammonia is to be condensed from the gaseous state, although a smaller vessel will suffice if ammonia is to be transferred as a liquid. The Dry Ice should be

put in first, and to this the organic liquid, usually isopropyl ether or acetone, should be added slowly. There is then less likelihood of the liquid bubbling over.

When the flasks are cooled by a liquid bath at $-80°$, the reflux condenser can be dispensed with. Even without the bath it is possible to carry out the entire experiment without outside cooling, although the formation of sodium acetylide is then so slow that a large amount of ammonia is lost. Even then, more ammonia may be added from the tank.

3. Use rubber stoppers. These should enter the neck of the flask about half way. The cork borer must be *sharp*. It should be approximately the size of the glass tubing or a trifle larger, since usually the opening, after boring, is smaller than the borer, owing to stretching of the stopper. The boring operation is performed as with cork stoppers, except that the pressure should be light and the borer should be lubricated. A satisfactory lubricant is caustic soda solution or preferably glycerol. The opening is cone-shaped if the pressure is too heavy.

4. Sodium hydroxide, potassium hydroxide, or soda lime can be used. Test the soda lime by heating a small amount in a test tube. If much water is expelled, dehydrate the portion to be used. Calcium chloride reacts with ammonia, expanding and becoming hot.

5. If a three-necked flask must be used, to one neck attach an addition tube (or wide Y tube) which permits attachment of condenser and inlet tube for acetylene. If a cooling bath is used, the reflux condenser can be dispensed with while the sodium solution is being transferred; however, a guarded opening to air must be provided.

6. A stirrer is necessary during the formation of sodium acetylide, because acetylene is not very soluble in liquid ammonia, and the solubility is decreased markedly by a rise in temperature or by the presence of dissolved sodium. The stirrer is desirable also during the reaction of sodium acetylide with *n*-butyl bromide, owing to the low solubility of sodium acetylide, but is not indispensable, since continual boiling of the liquid provides some agitation.

7. Owing to evaporation of ammonia some sodium is deposited in the tube. A smaller tube may become clogged.

8. Acetone is removed by concentrated sulfuric acid.

9. It takes only a few minutes to run in the ammonia as a liquid but much longer ($\frac{1}{2}$ to 1 hour) to condense the gas with the reflux condenser. The time for this last operation is lessened by using the liquid cooling bath.

10. *Caution:* Handle the sodium with tongs or with paper, and place it on a large piece of paper to catch all scraps, sodium oxide as well as metallic sodium. Do not allow these to come in contact with other objects such as desk top, floor, clothing, or skin. In case any is spilled, add some alcohol (*Caution:* flames), then some water, and then dilute aqueous acetic acid until no longer basic.

Do not throw pieces of metallic sodium, even scraps, into the sinks, but put them in alcohol, not in water, for sometimes sodium reacts explosively with water. After the reaction in alcohol has slackened, water may be added. When all reaction is over, pour the liquid down the hood sink in a good stream of water. Goggles are recommended as a safety measure.

11. From the density it is possible to approximate the desired size. Preferably weigh as one piece. Many pieces are not desirable, because of the large amount of exposed surface. If dissolving is slow at Dry Ice temperature, drop the bath so that the temperature will rise.

12. The solubility of acetylene in liquid ammonia is greatly diminished by dissolved sodium.

13. Or any higher primary alkyl bromide, in case a higher 1-alkyne is desired. Propyne and 1-butyne are gases at ordinary temperature. They can be purified by bubbling through much water and finally through dilute acid. They can be collected by condensing in a cold bath (see 2-Butene, Experiment 14–2).

14. A satisfactory setup consists of two flasks of about 2-liter capacity connected by means of a U tube reaching to the bottom of each. About 1 liter of water is added to the system. If the liquid becomes warm, apply cooling. If ammonia escapes freely from the system, replace the water, taking care not to lose any alkyne. If ammonia escapes through the seal of the stirrer, decrease the pressure head by raising the U tube. Note that heat is evolved when ammonia dissolves in water and that the resulting solution is lighter than water. Addition later of some butyl ether cuts down evaporation loss during handling.

15. Distillation is desirable, to be sure that no low-boiling constituent is present.

16. For alkynes above heptyne replace butyl ether with ethyl ether, which, however, is not satisfactory for the lower alkynes, owing to probable existence of azeotropic mixtures. Also, there may be difficulty of separating (as with pentyne).

17. Rearrangement may take place in contact with hot alkali solution.

18. The boiling points of 1-pentyne, 1-hexyne, and 1-heptyne are 40.2°, 71.4°, and 99.8°, respectively. Yield is about 40%.

19. This experiment is based on work of Vaughn, Hennion, Vogt and Nieuwland, *Jour. Org. Chem.*, **2**, 1 (1938).

Questions

1. Why is it desirable to exclude moisture?

2. Why not use calcium chloride in the guard tubes?

3. What is the boiling point of liquid ammonia?

4. What is the explanation for the blue color of the solution of sodium in liquid ammonia?

5. How does it happen that acetone may be present in the acetylene?

6. Why is the absorption of acetylene more rapid at the lower temperature?

7. Why is the amount of butyl bromide insufficient to react with the sodium acetylide?

8. What reaction (or reactions) take place when water is added to the reaction mixture?

9. Why is it desirable to add butyl ether?

10. What other liquids could serve here?

11. Explain why ethyl ether and 1-pentyne may be difficult to separate.

12. Explain how hydrochloric acid can remove ammonia from its solution in a nonmiscible organic liquid.

13. Do you think this separation can be made quantitative? Explain.

14. Explain why water may come over during the distillation at a temperature well below 100°.

15. What are the main impurities in the products?

16. State the steps taken to remove them.

17. Calculate ΔH for the hypothetical gas-phase reaction of acetylene and butyl bromide to give butyl acetylene and hydrogen bromide.

18. Starting with the data from Question 17, calculate ΔH for the reaction involving sodium metal, acetylene (gas) ,and n-butyl bromide (liquid) to form sodium bromide (solid) and n-butyl acetylene (liquid).

19. Calculate the amount of liquid ammonia that would be vaporized by the heat of the reaction mentioned in Question 18. State any assumptions made.

Experiment 15–2   Preparation of Acetylene

Properties of Acetylene (Note 1)

A PREPARATION. Support a *dry* 200-ml. distilling flask by means of a clamp. Fit a dropping funnel into the neck of the flask. To the side arm attach a tube leading to an empty wash bottle, where it should end just below the stopper. To the wash bottle attach a tube for collecting gas in vessels, over water. Place 10 g. of calcium carbide in the flask, and allow water to flow slowly, *drop by drop*, on the carbide. As soon as a sample of the gas collected in a test tube burns quietly when ignited, fill four 250-ml. bottles, and also a fifth bottle containing the amount of water equivalent to the theoretical volume of acetylene that will combine with 250 cc. of air (Note 2).

B COMBUSTION. Apply a lighted match to one bottle of the gas. In order to facilitate the removal of the gas, pour a stream of water into the bottle while the gas burns. Compare results with methane (or natural gas) and ethylene.

Apply a match to the mixture of acetylene and air.

C BAEYER TEST. Apply the potassium permanganate test for unsaturation to a second bottle of the gas. See Experiment 14–4.

D ADDITION OF BROMINE. Add 4 drops of bromine to another bottle of the gas, replace the cover, and invert the bottle slowly several times. If the color does not disappear within 1 minute, add to the bottle a few drops of sodium hydroxide solution, and shake. When the color has gone, examine the bottle for evidence of chemical change.

E FORMATION OF CUPROUS ACETYLIDE. Prepare cuprous chloride by adding to a solution of 6 g. of powdered cupric sulfate and 2 g. of sodium chloride in 20 ml. of hot water a solution of 1.5 g. of sodium bisulfite (or metabisulfite) in 10 ml. of 3 N sodium hydroxide. Cool. Allow the cuprous chloride to settle, and wash a few times by decantation. Add dilute ammonium hydroxide to form an ammoniacal cuprous chloride solution, of which any blue color is due to the presence of cupric ion. Add this solution to the fourth bottle of acetylene (Note 3).

Notes

1. *Caution: Acetylene is poisonous.* Do not allow acetylene to escape freely into the air. When through generating the gas, take the materials to the hood, add water to the flask and contents until the carbide is completely decomposed, dissolve the larger part of the residue by addition of dilute hydrochloric acid until the liquid is acidic, and wash the material down the sink in the hood, *not in the open laboratory sink.*

2. Show in your laboratory notes how you calculate this volume.

3. *Caution:* Cuprous and silver acetylides are dangerously explosive when dry. Wash all residues down the drain.

Questions

1. What is the purpose of the empty wash bottle?

2. Write equations for all reactions.

3. Which is more explosive, a mixture of ethylene and air or a mixture of acetylene and air? Explain.

4. What is the evidence of a chemical change in D?

5. The cuprous chloride reagent is a test for what radical?

6. What other reagent besides ammoniacal cuprous chloride could be used as a test?

7. What is a diolefin?

8. Calculate from bond energies alone:

   (a) ΔH of dehydrochlorination of an alkene chloride to form a chloroalkene.

   (b) ΔH of dehydrochlorination of the latter to form an alkyne.

9. Show how to calculate ΔH in the reaction of hydrogen chloride and potassium hydroxide. Does it have an influence on the reactions in 8?

10. Calculate values for dehydrobromination, as in 8, and compare with the results in 8.

11. What prediction can you make, based on ΔH values, about the equilibrium of the system acetylene, hydrogen bromide, and vinyl bromide (Table 15–1).

12. Calculate from free-energy values an equilibrium constant for the system, acetylene, ethylene, and hydrogen (as realized in the presence of a suitable catalyst).

13. What is a suitable catalyst for hydrogenating acetylene?

Chapter 16

ALKYL HALIDES

Alkyl halides are prepared most conveniently in the laboratory from the corresponding alcohols. Industrially alkyl chlorides, especially the amyl chlorides are prepared directly from the hydrocarbons by chlorination. Mixtures of halogen derivatives usually result. Alkyl halides also result from the reaction of hydrogen halides with olefins. A normal chain olefin yields ordinarily a secondary halide, and a "tertiary-base" olefin a tertiary halide. Although not an important laboratory method for preparing alkyl halides, the reaction is useful in terpene chemistry. In the presence of oxygen or of peroxides, however, the normal chain olefins may yield the primary halide.

If alcohols are the starting materials, the product consists of essentially a single halogenated hydrocarbon when the reagents employed are those that replace the hydroxyl group with a halogen atom. However, in some cases there may be a rearrangement, leading to the production of mixtures. This is noted especially in the case of isobutyl alcohol.

The reagents used may be (a) inorganic acid halides, especially those of phosphorus, for example phosphorus trichloride PCl_3, phosphorus tribromide PBr_3, and phosphorus pentachloride PCl_5; also thionyl chloride $SOCl_2$ and thionyl bromide $SOBr_2$; (b) mixtures of phosphorus and the halogen (seldom chlorine however); (c) the hydrogen halides, either anhydrous or in concentrated aqueous solution; or a combination of reagents which will generate the hydrogen halides, for example sulfuric acid and inorganic halides. The following examples are typical:

(a) $$3C_2H_5OH + PBr_3 \longrightarrow 3C_2H_5Br + P(OH)_3$$

$$CH_3(CH_2)_2CH_2OH + SOCl_2 \longrightarrow$$
$$CH_3(CH_2)_2CH_2Cl + SO_2 + HCl$$

(b) $$6C_2H_5OH + 3I_2 + 2P \longrightarrow 6C_2H_5I + 2P(OH)_3$$

(c) $$C_2H_5OH + HI \longrightarrow C_2H_5I + H_2O$$

$$CH_3(CH_2)_2CH_2OH + HBr \longrightarrow CH_3(CH_2)_2CH_2Br + H_2O$$

$$CH_3(CH_2)_2CH_2OH + HCl \xrightarrow{[ZnCl_2]} CH_3(CH_2)_2CH_2Cl + H_2O$$

$$(CH_3)_3COH + HCl \longrightarrow (CH_3)_3CCl + H_2O$$

$$C_2H_5OH + KBr + H_2SO_4 \longrightarrow C_2H_5Br + KHSO_4 + H_2O$$
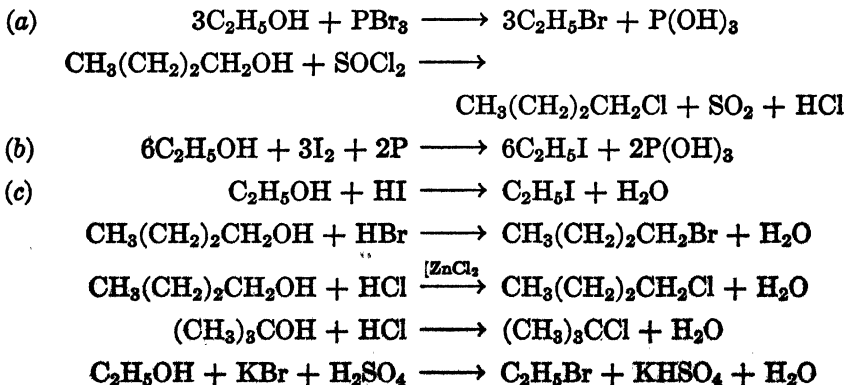
16.11 Alcohols and Inorganic Acid Halides. In method a the reactions usually are carried out by gradual addition of the acid halide to the alcohol, oftentimes in the presence of a suitable tertiary amine, such as pyridine. Usually the reactions, especially those of the lower alcohols, take place rapidly and exothermically. On this account careful control is desirable. A tertiary amine increases both these effects.

Side reactions may be quite extensive, especially in the case of phosphorus trihalides. The products of the side reactions are esters, such as phosphites and sulfites, or intermediate ester–acid halides. The extent of these side reactions is decreased by the presence of a suitable tertiary amine.

Yields of primary and secondary halides vary widely and may, under favorable conditions, be as high as 80 or 85%. Yields of tertiary halides (from tertiary alcohols) are better. Thionyl chloride and pyridine constitute one of the best reagents for converting alcohols to alkyl chlorides.

16.12 Alcohols, Phosphorus and a Halogen. In method b the halogen is added to a mixture of phosphorus and the alcohol. Red phosphorus is safer to use, although yellow phosphorus gives a faster reaction. Chlorine is seldom used this way. Bromine sometimes is used for making bromides, but not usually for simple alkyl bromides. The principal application of the use of phosphorus is with iodine, for by this combination smooth reaction takes place with alcohols, and the yields are good. The rate is satisfactory with methyl and ethyl alcohols but quite sluggish with the higher alcohols at room temperature. Since ΔH is negative, proper control must be maintained (see Chapter 1). Ethyl iodide (Experiment 16–2) is prepared from ethyl alcohol with red phosphorus and iodine.

Since phosphorous acid decomposes above 150°, reaction mixtures should not become too hot, as for example by direct-flame heating. Higher iodides do not mix with phosphorous acid, and often can be decanted after the reaction is over.

16.13 Alcohols and Hydrogen Halides. In method c usually an aqueous solution of the acid is used because of the greater convenience. In dilute aqueous solution little or no reaction takes place between an alcohol and a hydrohalic acid. Hydrochloric acid usually does not react with alcohols other than tertiary alcohols but usually does when sufficient zinc chloride is present. Hydrobromic and hydroiodic acids usually react. The reactions proceed best at the highest activity of the hydrogen halide and in the presence of water, since water accelerates the reaction. High activity of the acid may be realized by using an aqueous solution saturated at 0°, by passing the anhydrous acid into a

mixture of the alcohol and the concentrated acid, or, in the case of hydrobromic acid, by adding sulfuric acid.

The alcohol is heated with the hydrohalic acid, either under a reflux condenser until equilibrium is attained, or under conditions such that the alkyl halide can be distilled out of the reaction mixture as it is formed, as discussed later in connection with Experiment 16–1, The Preparation of Alkyl Bromides.

A combination of a metallic bromide, water, and sulfuric acid can be substituted for hydrobromic acid and often is used because of lower cost of materials and satisfactory yield. However, hydrochloric and hydroiodic acids usually cannot be replaced by similar combinations, because hydrochloric acid alone does not react with many alcohols, especially primary alcohols, and because hydroiodic acid is oxidized by sulfuric acid.

16.14 Thermochemistry. In the gas-phase reaction of an alcohol with an anhydrous hydrogen halide, calculation from bond energies gives values of ΔH as follows: with hydrogen chloride, -4.0 kcal., with hydrogen bromide, -8.9 kcal.; and with hydrogen iodide, -14.3 kcal. The reactions therefore are moderately exothermic.

For the reaction producing ethyl bromide, ΔF in the gas phase is -7.6 kcal., and in an aqueous solution, $1\ M$ in hydrobromic acid and in alcohol, it is $+7.6$ kcal. This shows the enormous influence of water on this reaction, since ΔF of formation of the reactants decreases in aqueous solution 15 kcal. more than does ΔF of formation of the products. This results largely from the fact that ΔF of formation of anhydrous hydrogen bromide is -12.5 kcal., and of aqueous $(1\ M)$ hydrobromic acid is -24.6 kcal. In a solution saturated with a hydrogen halide, the free-energy change approaches that calculated for the gas-phase reaction.

16.15 Equilibrium. The equilibrium constant (Equation 1–30) calculated for the gas-phase reaction is 17,000 and for the reaction in $1\ M$ aqueous solution is 5.9×10^{-5}. This shows that in the former case ethyl bromide is favored and in the latter case ethyl alcohol is favored. As the concentration of hydrobromic acid in aqueous solution increases above $1\ M$, the equilibrium constant approaches a value almost as large as that in the gas-phase reaction.

Since in the reactions of ethyl alcohol with hydrogen halides the heat evolution increases in the order:

$$\text{Chlorides} < \text{bromides} < \text{iodides}$$

the equilibrium constants probably increase in the same order, unless the respective values for the $T\Delta S$ term of Equation 1–29 increase in the

opposite order to ΔH. Just as in the case of hydrobromic acid, water has a profound effect on the activities of hydrochloric and hydroiodic acids.

The equilibrium constant between the alcohol, hydrogen bromide, alkyl bromide, and water is increased by the presence of sulfuric acid, which increases the activity of the hydrogen bromide. The effect in decreasing the activity of the alcohol is compensated by the decrease in the activity of water. Thus it is possible to get a good yield of n-butyl bromide by refluxing equimolal amounts of n-butyl alcohol and potassium bromide, if a total of about 2 moles of sulfuric acid (with water to make 80% acid) is present. The forward reaction is favored by the insolubility of the alkyl bromide in the reaction mixture. The reaction can be driven further towards completion by distilling out the alkyl bromide as it is formed (see 1.25).

16.16 Rates. The order of reactivity of hydrohalic acids (excluding hydrofluoric acid, which is essentially nonreactive) is

$$HI > HBr > HCl$$

with a given alcohol. The order of reactivity of alcohols is

$$\text{Tertiary} > \text{secondary} > \text{primary}$$

with a given hydrohalic acid. Thus, the fastest rates are those between tertiary alcohols and hydroiodic acid. The slowest are those between primary alcohols and hydrochloric acid. Tertiary alcohols react rapidly with concentrated hydrochloric acid at room temperature, as in Experiment 16–4, The Preparation of Tertiary Butyl Chloride. Primary alcohols react only very slowly at room temperature, even with hydriodic acid. Primary alcohols react slowly with hydrobromic acid when heated, but rapidly enough to give good yields of bromides. They react only slightly with hydrochloric acid, even when heated in a sealed tube.

Often a catalyst is added to increase the rate of reaction of hydrochloric or hydrobromic acid with an alcohol. Zinc chloride is commonly used with hydrochloric acid, as in Experiment 16–3, The Preparation of Secondary Butyl Chloride, and sulfuric acid with hydrobromic acid. The acceleration of the reaction in both cases is the result of two effects, a catalytic effect and an increase in the activity of the dissolved hydrogen halide. Usually a rather large amount must be added. Thus to make primary chlorides, the alcohols are heated with concentrated hydrochloric acid previously saturated with anhydrous zinc chloride at 0°. For primary bromides a convenient reagent containing hydrobromic acid, sulfuric acid, and water is obtained by passing sulfur diox-

ide into a mixture of bromine and water. In Experiment 16–1, General Method of Preparing Alkyl Bromides, in which hydrobromic acid is obtained from potassium bromide, sulfuric acid, and water, an excess of sulfuric acid is desirable.

16.17   General Method for the Preparation of Alkyl Bromides.
All lower primary alkyl bromides up to and including n-amyl bromide and many secondary alkyl bromides have lower-boiling points than the corresponding alcohols. Thus, such a bromide can be distilled from the reaction mixture as an azeotropic mixture with water and the alcohol. In this way the reaction can be driven to completion. This is the basis for Experiment 16–1, The General Method of Preparing Alkyl Bromides. Here potassium bromide, sulfuric acid, water, and alcohol comprise the reaction mixture. The mixture is distilled slowly through a fractionating column so as to obtain the ternary azeotropic mixture by driving over the desired alkyl bromide as it is formed. (Refer to Section 9.2, Fractionation of Nonideal Solutions.)

The alcohol which distils with the bromide can be removed by shaking the bromide with cold sulfuric acid, 65 to 80%. The acid is returned to the boiler and an additional amount of the bromide obtained. Thus the sulfuric acid serves a double purpose, for it also aids in the purification of the product by removing the main impurity.

The principal side reaction is the formation of an olefin. Less important reactions are ether formation, polymerization (darkening), and oxidation by the sulfuric acid. All of these are diminished by diluting the reaction mixture with water. However, even in dilute acid solution tertiary alcohols undergo dehydration when heated (see Chapter 14). Consequently this method is not satisfactory for the preparation of tertiary bromides. Secondary alcohols undergo dehydration when heated with 65% sulfuric acid (see Table 14–2). Consequently, the bromide reaction must be carried out in a more dilute sulfuric acid, usually 50 or 55%, *and as fast as possible*.

Allyl alcohol undergoes marked polymerization in 65% sulfuric acid, but only slight in 55% acid.

The advantages of this method are the following: (1) The reaction is driven to completion by the removal of the product as it is formed; (2) the reaction can be carried out more rapidly than by the refluxing process since the reverse reaction of the bromide with water is thus diminished by its continual removal as formed; (3) alcohols that give a rearranged bromide by the refluxing method (isobutyl alcohol gives *tert*-butyl bromide) give the corresponding bromide by this method, since the time of exposure to the acid is short; (4) ether formation is not troublesome, because, with the exception of methyl and ethyl ethers,

ethers boil above the corresponding bromide and are largely returned to the boiler by the fractionating column. Any that distils will be removed from the product later by the extraction treatment with sulfuric acid and returned to the boiler, where it finally will be reconverted to alcohol (see discussion, Chapter 22).

The precautions to observe in this method are: (1) With primary alcohols the initial molar ratio of sulfuric acid to metallic bromide should exceed unity; otherwise, the rate is low; (2) with secondary alcohols this ratio should be about unity; otherwise, unsaturation may result; (3) the metallic bromide should be in excess (5% or higher) over the alcohol if it is desired to obtain a good yield on the alcohol basis; (4) water must be present in the original reaction mixture, in order to minimize the undesirable reactions of concentrated sulfuric acid on alcohols and to increase the solvent power of the mixture for hydrogen bromide; (5) too much water should not be present since dilution adversely affects the reaction; (6) agitation is desirable during the initial heating so as to keep in solution the hydrogen bromide formed and to minimize caking; (7) the fractionation should be efficient, so that the distillate will have a composition approximating that of the constant-boiling mixture, since this brings over the least amount of alcohol; (8) sulfuric acid used for washing the crude bromide should not be too concentrated, that is, not more concentrated than about 80% by weight, because concentrated sulfuric acid sometimes decomposes alkyl bromides and also because the phases separate better when some water is present; (9) this sulfuric acid should not be too dilute, probably not less than 70%, when one is working with C_5 or higher compounds; otherwise, the alcohol will not be well extracted from the bromide.

In order that the bromide may be distilled as it is formed, so as to contain the minimum amount of alcohol, the distilling temperature should be that of the azeotropic ternary mixture. Table 16–1 shows the composition and the boiling temperatures of the various azeotropic mixtures, binary and ternary, which are possible in systems composed of two or more of these components, water, alcohol, and the corresponding bromide; also, the composition of each phase of the ternary mixture. Since hydrobromic acid is volatile also, the distillates may contain a small amount of this acid. They would then be quaternary rather than ternary mixtures.

Different members of the class will carry out the preparation of different alkyl bromides, for example ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, and a few amyl bromides, by suitable modifications of the method described for isobutyl bromide. Allyl bromide should be prepared also. A separate report must be made, as

TABLE 16–1

DISTILLING TEMPERATURES OF ALCOHOLS AND ALKYL BROMIDES; DISTILLING TEMPERATURES AND COMPOSITIONS (PERCENTAGES BY WEIGHT) OF AZEOTROPIC MIXTURES OF ALCOHOLS, BROMIDES, AND WATER

	n-Propyl	Iso-propyl	n-Butyl	Iso-butyl	s-Butyl	n-Amyl	Iso-amyl
Pure Compounds							
Alcohols							
Temperature,* °C.	97.8	82.5	117.8	108.0	99.5	137.9	132.0
Bromides							
Temperature,* °C.	70.8	60	100.3 †	91.5	91.3	128.7 ‡	120.4 §
Binary Mixtures							
Alcohol–Bromide							
Temperature,‖ °C.	67.9	57.0	97.90	88.4?	86.5	125	117
Alcohol, %	6.6	7.4	12.34	10.1?	18.7	26?	15.7
Alcohol–Water							
Temperature, °C.	87.7	80.4	92.4	90.0	88.5	96.0	95.2
Water, %	28.3	12.1	38	33.2	32.1	54.0	49.6
Bromide–Water							
Temperature,‖ °C.	62.2		79.5	75.0	74.1	89.2	86.7
Water, %	4.1		10.9	9.1	9.0	22.5	20.2
Ternary Mixtures							
Temperature,‖ °C.	62.1	53.2	79.3	74.5	73.7	88.9	86.5
Upper phase, %	4.3	3.75	11.5	8.7	7.6	18.2	16.1
Alcohol in upper phase, %	9.3	14.5	2.3?	4.4	7.8	2.3?	1.1–1.3
Bromide in upper phase, %	0.6	0.6	0.1?	0.1	0.4	0.1	0.2
Alcohol in lower phase, %	3.7	2.9	5.6	4.1	2.3	8.5	6.6
Water in lower phase, %	0.3	0.3	0.2	0.3	0.3	0.3?	0.35
Alcohol, overall, %	3.9	3.8	5.3	4.2?	8.3	11.1	5.7
Water, overall, %	4.2	3.2	11.4	8.6	7.3	18.0	16.2
Bromide, overall, %	91.9	93.0	83.3	87.2?	84.4	70.9	78.1

* At 760 mm. except when noted otherwise.
† At 746 mm.   § At 745 mm.
‡ At 739 mm.   ‖ At 742 to 745 mm.

well as the write-up in the notebook. The report should show all the experimental details, especially the amounts of materials in grams and in moles, the molal ratios, details of the procedure, such as distilling temperatures, and comments on the procedure.

Experiment 16–1   General Method of Preparing Alkyl Bromides

Isobutyl Bromide (Notes 1, 2, and 3)

Equip a 0.5-liter round-bottomed flask with a Claisen-top fraction-ating tube (Figure 9–4E) provided with a reflux condenser, and attach a condenser for distillation. In order to obtain the azeotropic mixture smoothly as the bromide is formed during the experiment, the length of packing in the tube should be at least 40 cm., and to prevent flooding the tube should be at least 25 mm. in diameter (Note 4).

In the flask, disconnected for the purpose, *thoroughly* mix 1.5 to 1.7 mole of cold 65 to 70% (by weight) sulfuric acid (Notes 5 and 6) with 1.00 mole of anhydrous isobutyl alcohol (Note 7). Add in portions, with swirling to minimize caking, 1.05 mole of finely granular potassium bromide. Afterwards apply heat with a spreading, slightly luminous flame, so as to avoid excessive local heating while much solid is present. Later, more air may be admitted to the burner. During the initial heating, swirl constantly to minimize caking and to promote reaction between potassium bromide and sulfuric acid. After the potassium bromide has largely dissolved, or after the mixture becomes so hot that hydrogen bromide or alkyl bromide escapes from the flask, attach the flask to the apparatus. Continue the heating. If evolution of hydrogen bromide is marked and continues for 4 or 5 minutes, add more (10 to 20%) of the dilute sulfuric acid and mix *thoroughly*.

Distil a two-phase distillate of isobutyl bromide, isobutyl alcohol, and water *as rapidly as possible*, while keeping the distilling temperature reasonably close to (1° to 5° above) the distilling temperature of the ternary azeotropic mixture (Note 8). Continue so long as the azeo-tropic mixture distils. When the temperature of distillation rises too high, reduce the size of the flame just enough to stop the distillation but not the refluxing. After 5 to 10 minutes, continue the distillation as before. This technique allows alkyl bromide to accumulate when it forms slowly. When it is not possible to distil any more of the con-stant-boiling mixture, stop the distillation. Usually 1 to 2 hours' heating is necessary. Leave the reaction mixture in the flask.

Separate the two phases of the distillate in a separatory funnel, and shake the organic phase (Note 9) with 0.2 to 0.4 mole of cold 65 to 70%

sulfuric acid, divided into two portions, and record the weight of crude bromide. Place the sulfuric acid extracts in the reaction flask, reflux for 5 or 10 minutes, distil as before, and again obtain an azeotropic mixture containing isobutyl bromide. Shake this distillate with sulfuric acid, as before (Note 10).

Weigh the separate fractions of the bromide, and combine them. Shake the liquid in a separatory funnel two or three times with water to remove most of the acid present, using two separatory funnels for convenience (refer to 6.17). Remove any halogen and all remaining acid with dilute aqueous sodium carbonate (refer to 6.13 and 6.16), and wash finally with water to remove sodium carbonate. Shake the organic phase with a small amount of suitable drying agent (potassium carbonate or calcium chloride) so as to dry in stages (refer to 12.26), removing the aqueous phase, and repeating. If the liquid must stand for a time, run it into a small conical flask, and add a little more of the drying agent. Let stand until water is well removed (Note 11). Remove the drying agent by proper filtration (refer to 12.28) into a dry distilling flask of suitable size (refer to 7.11) attached to a small dry water-cooled condenser.

Distil slowly with a *small* flame, so as to distil over completely at the beginning any water remaining, thus completely drying the main portion of the product (refer to 12.12). Collect separately in a small flask the first, cloudy distillate. Stop when the distilling temperature is constant and/or water no longer comes over. Remove water from the distillate and also from the cooler part of the distilling apparatus where it has condensed. Add the dried liquid, and continue with the distillation. If the distillate is cloudy, repeat. Collect a clear distillate in a 5° range near the boiling point of the expected compound.

Determine the percentage yield of crude and of pure isobutyl bromide from the alcohol. Label the product properly, with name, boiling point, yield, name of experimenter, and date. Complete the write-up of the experiment, and report to the instructor (Note 12).

Notes •

1. Other alkyl bromides may be prepared, with some other alcohol replacing isobutyl alcohol. With other similar primary alcohols, for example, n-propyl and n-butyl alcohols, the same amount and same concentration of sulfuric acid are satisfactory. A larger amount of acid (1.8 to 2 moles) usually is desirable with n-amyl and isoamyl alcohols. With lower alcohols the acid preferably can be more concentrated owing to greater solubility of hydrogen bromide in the lower alcohols. With n-propyl alcohol use 75% sulfuric acid; with ethyl alcohol use 75 to 80% sulfuric acid and a larger amount, 1.8 to 2 moles. (See Note 2 for methanol.)

With secondary alcohols, for example, isopropyl and secondary butyl alcohols, use 1.0 mole of 50 to 55% acid. Since these alcohols dehydrate easily (see Experiments 14–2 and 14–3), it is desirable to convert sulfuric acid to potassium bisulfate as rapidly and as completely as possible, with continuous whirling while heating, before attaching to the apparatus. Distil the alkyl bromide as rapidly as possible, even if several degrees above the distilling temperature of the azeotropic mixture. If the experiment is carried out too slowly, the temperature will be *below* that of the mixture, owing to the presence of some olefin.

With allyl alcohol, carry out all operations, including cleaning of the apparatus, in the hood, since allyl bromide is a lachrymator. Use about 1.5 moles of 50 to 55% acid. Since an important side reaction is polymerization, due to the sulfuric acid, carry out the reaction rapidly. Convert sulfuric acid quickly to potassium bisulfate with continuous agitation, heat rapidly to the distilling temperature, and distil the bromide as rapidly as possible.

2. For the preparation of the gaseous bromide, methyl bromide, the reaction proportions are altered somewhat, and the apparatus is modified by:(1) providing the generating flask with a safety tube, (2) replacing the fractionating column by a reflux condenser (refer to 7.23) and a purifying train, and (3) replacing the receiving flask by an ampoule. A good fractionating column actually is better than a reflux condenser, since less alcohol is carried over.

The reaction mixture is 0.50 mole of potassium bromide, a 20% excess of methanol, and a 100% excess of 75 to 80% sulfuric acid. (Refer to the equation and Notes 5 and 6.)

The safety tube, purifying train, and collecting ampoule are described in Experiment 14–2, The Preparation of 2-Butene. However, the train need consist of only three wash bottles, the first for water and the second and third for concentrated sulfuric acid. As in Experiment 14–2, the generating flask and condenser should be closed by cork stoppers, as practice in cork boring (unless already a similar apparatus has been constructed satisfactorily). Be sure you know how to bore a stopper satisfactorily by getting one air-tight, before proceeding with the next. The apparatus must be approved by the instructor for air tightness before you continue.

When heat is applied to the reaction mixture, methyl bromide is evolved, the rate depending on the temperature. Since a fractionating column, if efficient, will return condensable vapor of methanol, the train as described should suffice to purify the gas, even at a rapid rate of flow. In general, follow the directions of Experiment 14–2. The yield of methyl bromide is 85%.

3. In the table of properties of compounds, which should be made before the experiment is started, show the number of grams of all substances taken, as well as the number of moles of reactants (see page 2). Show also the amounts of sulfuric acid and water taken for the diluted acid and the concentration of the diluted sulfuric acid. Show the constants of the azeotropic mixtures involved.

4. The length of packing is based on using glass rings, approximately 5 mm. × 5 mm. A slightly longer packing (45 or 50 cm.) often performs more smoothly. For more volatile bromides the column should be somewhat longer and for less volatile it may be shorter, as for example not less than 35 cm. for n-butyl bromide. (Refer to 9.14 and Section 9.2.)

5. *Caution:* Concentrated sulfuric acid is corrosive. Any spilled on hands, clothing, desks, or floor should be diluted at once with water and at once neutralized with sodium bicarbonate solution. When diluting to 65 or 70% add the acid to water, mixing *thoroughly*, preferably by whirling while cooling under the tap. Make up a

sufficient amount for the entire experiment. Unless the composition of the concentrated acid is known for certain, determine the density. Check calculations with the instructor.

6. With this amount of diluted acid the escaping tendency of hydrogen bromide during the initial heating period is about as great as desired. It may become too great, with consequent loss of hydrogen bromide, if the amount of the diluted acid is smaller, or if the acid is more concentrated; it becomes less, with consequent drop in reactivity, if the amount of diluted acid is greater, or if more water is added. If hydrogen bromide escapes freely during the initial phases of heating, add more (10 to 20%) of the diluted acid. Addition of water alone is not recommended, since then the rate of reaction may drop too much.

7. Test for dissolved water by shaking for a few minutes with a small amount of anhydrous potassium carbonate. The solid should not become pasty or liquefy.

8. As the temperature rises, the percentage of alcohol in the distillate increases.

9. Reference to Table 16–1 shows that the amount of alcohol dissolved in the aqueous phase is insignificant, relative to the total amount of alcohol taken.

10. Return the acid to the reaction flask for recovery of more bromide if you believe that 5% or more of the alcohol has not reacted.

11. Recall the discussion on the value of the drying couple $K_2CO_3 \cdot 2H_2O$-saturated solution. In case sulfuric acid is still present, finely divided calcium sulfate is formed if calcium chloride is added.

12. Yields: isobutyl bromide, 75%; n-butyl bromide, 85%; n-amyl and isoamyl bromides, 85%; ethyl bromide, 80%.

Questions

1. Assuming that you would obtain, in a large-scale industrial production of the alkyl bromide, the same percentage yield as in this small-scale experiment, calculate the cost of the chemicals necessary to produce 1 kg. of same. Show the prices of the raw material, as obtained from current market lists (See *Chemical and Engineering News*).

2. Why does dilution with water much below 65% adversely affect the reaction?

3. Why is some excess of sulfuric acid desirable in the preparation of primary bromides?

4. Why is an excess of sulfuric acid undesirable in the preparation of secondary bromides?

5. Why should any water be present?

6. What are possible side reactions?

7. How can they be minimized?

8. To what extent do you judge that bromide formation had taken place by the end of the first distillation? Give reasons for your answer.

9. If the function of the fractionating column is the return of alcohol to the boiler, why not use a reflux condenser to accomplish this?

10. Why not shake the isobutyl bromide with water in which isobutyl alcohol is somewhat soluble, for the purpose of removing the alcohol?

11. What is the ratio of the weight of alcohol lost in the upper aqueous phase to 100 g. of bromide in the heavier phase?

12. Which of the different alcohols is lost most in the aqueous phase?

13. By what other methods may the alkyl bromide be prepared? Write the equations for the reactions.

14. What undesirable side reactions may arise from the action of hot concentrated sulfuric acid on alcohols?

15. If ethyl bromide were being prepared, instead of butyl bromide, what would be the main impurity of the crude product?

16. How could it be removed?

17. What is the function of the wash bottle containing water in the methyl bromide experiment?

18. What are the main impurities in the crude and final product?

19. State the steps taken to remove them.

Experiment 16-2   General Method of Preparing Alkyl Iodides

Ethyl Iodide

In a flask of about 200 ml. capacity put the amount of red phosphorus that is 10% in excess and absolute ethyl alcohol that is 20% in excess of the amount that reacts with 0.30 mole of iodine (Notes 1 and 2). Add the iodine to the mixture during the course of 15 to 20 minutes, and cool the flask moderately from time to time in water from the tap in case the heat of the reaction raises the temperature so high that loss by volatilization is possible (Note 3).   In order to complete the reaction, heat the flask on a constant-level hot-water bath for 2 hours under a short reflux condenser (refer to 7.23) with a calcium chloride tube attached to the top of the condenser, supplying heat just sufficient to cause gentle boiling and moderate refluxing (Note 4).   Or the mixture may be allowed to stand, protected by the calcium chloride tube, until the next laboratory period.

Distil the product through a condenser (arranged for distillation) attached by a short bent tube not less than 8 mm. inside diameter.   Heat by means of a vigorously boiling water bath or by an oil (wax) bath starting at about 80° and gradually increasing in temperature to 110° or 120°.   If the water bath is used, it will be necessary, at the last, to heat the bare flask for a short time with a luminous flame kept in constant motion (Note 5).

Shake the liquid in a separatory funnel two or three times with water to remove most of the acid present (Note 6), using two separatory funnels for convenience (refer to 6.17).   Remove any halogen and all remaining acid with dilute aqueous sodium carbonate or hydroxide (refer to 6.13 and 6.16), and wash finally with water to remove sodium carbonate.   Shake the organic phase with a small amount of suitable drying agent (potassium carbonate or calcium chloride) so as to dry in stages (refer to 12.26), removing the aqueous phase, and repeating.   If the liquid must stand for a time, run it into a small conical flask, and add a little more of the drying agent.   Let stand until water is well removed (refer to 12.26).   Remove the drying agent by proper filtration

(refer to 12.28) into a dry distilling flask of suitable size (refer to 7.11) attached to a small dry water-cooled condenser.

Distil slowly with a *small* flame (Note 7), so as to distil over completely at the beginning any water remaining, thus completely drying the main portion of the product (refer to 12.12). Collect separately in a small flask the first, cloudy distillate. Stop when the distilling temperature is constant and/or water no longer comes over. Remove water from the distillate and also from the cooler part of the distilling apparatus where it has condensed. Add the dried liquid, and continue with the distillation. If the distillate is cloudy, repeat. Collect a clear distillate in a 5° range near the boiling point of the expected compound.

Label the product, showing name, boiling-point range, weight in grams, percentage yield, and date; complete the write-up of the experiment, and report to the instructor (Note 8).

Notes

1. Collect pertinent data in the form of a table before proceeding (page 2).

2. In the case of the cheaper alcohols, the aim should be the maximum yield on the iodine basis. For this reason a larger excess of ethyl alcohol may be taken.

3. Recall the necessity of avoiding accumulation of reactants when the reaction is exothermic, if there is no heat effect after addition of the first portions of iodine have been made. Higher alcohols, reacting more slowly, should be heated, as the iodine is added.

4. A refluxing temperature is both desirable and satisfactory with *n*-propyl and *n*-butyl iodides. For the latter an oil bath is recommended.

5. The oil (wax) bath is more convenient than a boiling-water bath. See discussion about the decomposition of phosphorous acid. With *n*-butyl or higher iodide decant the organic phase from phosphorous acid and unchanged phosphorus. Steam distillation is another excellent procedure with *n*-butyl iodide. Add much water, and distil quickly through a short wide exit tube (refer to Chapter 10).

6. Or shake two or three times with cold sulfuric acid, 70 to 80% (refer to Experiment 14–2, Note 3). Then shake with water three or four times. This modification is necessary with higher iodides, owing to probable presence of unreacted alcohol. Since sulfuric acid may react slowly with the iodide, do not prolong the operation. In the case of secondary and tertiary iodides use the more dilute acid.

7. Since high primary alkyl iodides decompose at the high temperature required for their distillation at atmospheric pressure, vacuum distillation is desirable. In the case of secondary and tertiary iodides this is necessary.

8. Yield: ethyl, *n*-propyl, or *n*-butyl iodide, 80 to 90%.

Questions

1. Assuming that you would obtain, in a large-scale industrial production of ethyl iodide, the same percentage yield as in this small-scale experiment, calculate the cost of the chemicals required to produce 1 kg. of ethyl iodide. Show prices of raw

materials as obtained from current market lists (see *Chemical and Engineering News*).

2. What is the objection to having the reaction mixture boil vigorously?

3. Why is the product shaken many times with water?

4. Is this method of preparing ethyl iodide any better than preparing it from alcohol, potassium iodide, and concentrated sulfuric acid? Explain.

5. By what other method may ethyl iodide be prepared conveniently? Write the equation.

6. Why is any excess of alcohol added?

7. Why is such a large excess added?

8. If *n*-butyl iodide were prepared, would an excess of alcohol be advantageous or not?

9. Do you believe that this reaction is easily reversible as the hydrobromic acid-alcohol reaction is? Give reason for your answer.

10. What impurities may be present in the crude and final products?

11. What steps have been taken to remove them?

Experiment 16–3   General Method of Preparing
Secondary Alkyl Chlorides

Secondary Butyl Chloride (2-Chlorobutane)

In a 500-ml. distilling flask place the amount of c.p. concentrated hydrochloric acid (sp. gr. 1.19) that contains 1.5 moles of hydrogen chloride (Notes 1 and 2). Surround the flask with ice and water, and add gradually with *shaking* and *cooling* 0.5 to 1.0 mole of technical anhydrous zinc chloride (Notes 3 and 4). The zinc chloride should be weighed out in a flask and kept well stoppered. Add 0.5 mole of anhydrous secondary butyl alcohol (2-butanol, Note 5), mix *thoroughly* by swirling, and attach to the flask a thermometer and a long condenser for distillation (see Figure 7–1). Heat slowly with a small flame. As soon as hydrogen chloride is evolved, lower the flame, and maintain the liquid at a temperature just short of distillation, to allow butyl chloride to form. Finally, after about 0.5 hour, or when the upper liquid phase no longer increases in volume, distil over the butyl chloride. So long as butyl chloride is present as a separate layer in the reaction flask, the distillation can be carried out with moderate rapidity. In case much hydrogen chloride is evolved, have the adapter dip under ice water.

Without needless delay shake the organic phase twice with ice water in a separatory funnel, twice with ice-cold 75% (by weight) sulfuric acid, at least twice again with ice water, and then with cold aqueous sodium carbonate until the organic phase is neutral to moist litmus paper.

Wash with cold water again, separate, and remove residual water in

stages with small amounts of anhydrous potassium carbonate (refer to 12.26) while shaking in the separatory funnel, until the solid is pasty. Only after the water is well removed, may the product be allowed to stand (Note 6). Transfer to a conical flask with some additional drying agent if the experiment cannot be completed the same day (Note 7).

Remove the drying agent (refer to 12.28), and distil slowly with a microflame from a suitable dry distilling flask (refer to 7.11) attached to a dry water-cooled condenser. In case the distillate is cloudy, continue the distillation until the liquid drops off clear, thus drying the main portion of the product by distillation (refer to 12.12). Recombine, after removing water from the wet portion, and continue.

Collect the fraction which boils within a 5° range near the boiling point of this butyl chloride. Label the product, showing name, boiling-point range, weight in grams, percentage yield, and date. Complete the write up of the experiment, and report to the instructor.

Notes

1. Collect pertinent data in the form of a table (page 2).
2. It is desirable to use the most concentrated hydrochloric acid (1.19) available. Since technical hydrochloric acid usually is less concentrated than the c.p. grade, the latter has been specified.
3. Care should be taken to avoid needless loss of hydrogen chloride by the liquid becoming warm. It is not necessary that all of the zinc chloride dissolve. After about 0.8 mole has dissolved, the dissolving of the remainder is quite slow. The technical powder dissolves more readily than do sticks.
4. The yield is about 80% with 0.5 mole and 88% with 1 mole.
5. Test for water by shaking with a *small* amount of potassium carbonate. If the alcohol is not anhydrous, the yield is low for two reasons: (1) less alcohol taken than calculated; (2) dilution of the hydrochloric acid.
6. Slow hydrolysis takes place if the product stands with water.
7. Keeping the liquid in the separatory funnel with drying agent is not advisable.

Questions

1. Assuming that you would obtain, in a large-scale industrial production of secondary butyl chloride, the same percentage yield as in this small-scale experiment, calculate the cost of the chemicals required to produce 1 kg. of the same. Show prices of raw materials as obtained from current market lists. (See *Chemical and Engineering News.*)
2. Why is a large excess of hydrochloric acid necessary?
3. Why is *sec*-butyl chloride shaken with water?
4. Why is *sec*-butyl chloride shaken with 75% sulfuric acid?
5. Why not use concentrated sulfuric acid?
6. Why is *sec*-butyl chloride shaken with sodium carbonate solution?
7. What is the main impurity dissolved in the butyl chloride after shaking with anhydrous potassium carbonate?

8. How may this impurity be removed?

9. Why is it not advisable to let liquid and drying agent stand in the separatory funnel?

10. Why not prepare *sec*-butyl chloride by the action of potassium chloride and concentrated sulfuric acid on the alcohol?

11. List the three classes of alcohols in the order of their reactivity with strong acids.

Experiment 16–4   Preparation of Tertiary Butyl Chloride
(Notes 1 and 2)

In a separatory funnel shake together for a few minutes 0.50 mole of anhydrous *tert*-butyl alcohol (Note 3) and the amount of c.p. concentrated hydrochloric acid (sp. gr. 1.19) that contains 1.5 moles of hydrogen chloride. Let stand for 15 to 20 minutes for separation of the two phases, draw off the aqueous phase, and shake the organic phase two or three times with ice-cold water. Then, without needless delay, shake with cold dilute (about 5%) sodium bicarbonate solution until the organic phase is neutral to moist litmus paper. From here on, follow the directions of Experiment 16–3, third and subsequent paragraphs (Notes 4 and 5).

Notes

1. This method can be employed also in the preparation of tertiary amyl chloride.

2. Collect pertinent data in the form of a table (page 2).

3. In case the alcohol contains water (as the constant-boiling mixture), make correction for the amount of water, and take a larger excess of hydrochloric acid.

4. *tert*-Butyl chloride hydrolyzes more rapidly than *sec*-butyl chloride.

5. Yield is 85%.

Questions

1. Why is the *tert*-butyl chloride shaken with water?

2. Why is the *tert*-butyl chloride shaken with sodium bicarbonate solution?

3. Why not prepare this chloride by the action of potassium chloride and concentrated sulfuric acid?

4. Give the formulas and names of the butyl chlorides.

5. Which of these reacts most rapidly with water?

6. Is the reaction between *tert*-butyl alcohol and hydrochloric acid reversible?

7. Why is an excess of hydrogen chloride taken?

8. Is there any noticeable heat effect in this reaction? Explain.

9. What are the probable impurities in the crude and final products?

10. State the steps that have been taken to remove them.

11. Why is it not advisable to let liquid and drying agent stand in a separatory funnel?

Experiment 16–5   Properties of Alkyl Halides

A TEST FOR HALOGEN (NOTE 1). Make a small loop (1 to 2 mm. diameter) at the end of a piece of copper wire, and heat in a flame until the flame remains colorless. Collect a little of an organic halogen compound on the loop, and heat again. A green color is characteristic of halogen compounds. Compare with the result obtained when the test is repeated separately with nitric and hydrochloric acids (Note 2).

B REACTION WITH SILVER NITRATE. Add from droppers similar volumes (2 or 3 drops) of ethyl bromide, ethyl iodide, sec-butyl chloride, and tert-butyl chloride to separate 5-ml. portions of an alcoholic solution of silver nitrate. The alkyl halides must be free of acid. Shake, and note any change. Stopper the test tubes, and allow to stand for about 0.5 hour, with an occasional shaking. Note and explain any change. Compare with the reaction of a saturated alcoholic solution of potassium iodide with silver nitrate.

C REACTION WITH ALCOHOLIC POTASSIUM HYDROXIDE. Add 2 to 3 drops of ethyl bromide to 10 ml. of alcoholic potassium hydroxide, and boil *gently* for about 1 minute. Dilute with distilled water, acidify with c.p. nitric acid, and add a few drops of aqueous silver nitrate.

D REACTION WITH SODIUM. To 3 ml. of ethyl bromide in a dry test tube, add a small piece of sodium with bright freshly cut surfaces. Close the tube with a cork stopper carrying a small drying tube containing calcium chloride, and set aside. Examine from time to time for evidence of chemical change. After it has stood for a day, heat gently to drive off the ethyl bromide, add 2 to 3 ml. of alcohol to the residue to decompose sodium *completely*, dilute with 10 ml. of distilled water, add dilute c.p. nitric acid until acid, and test for bromide ion.

E HYDROLYSIS OF ALKYL HALIDES. Add a few drops of neutral ethyl bromide, ethyl iodide, sec-butyl chloride, and tert-butyl chloride to a few milliliters of neutral water. Shake, and then test the liquid with neutral litmus paper and universal indicator paper. Repeat at intervals in case no change is noted. Arrange the alkyl halides in the approximate order of reactivity in this reaction.

F FORMATION OF A GRIGNARD REAGENT. Thoroughly clean the surface of a piece of magnesium ribbon about 150 mm. in length, cut it into small pieces, and place these in a dry test tube, preferably not smaller than 20 mm. in diameter. Add 1 ml. of ethyl bromide and 2 ml. of *absolute* ether. Rub the surface of the magnesium with a stirring rod. Soon the ether should start to boil. If the boiling is too vigorous, cool moderately; otherwise, ether is lost before complete reaction takes place. If no reaction takes place, heat very *gently* (do not boil). If

there is still no action, add a small crystal of iodine (Note 3). Let stand until most of the magnesium has disappeared. Close with a loosely fitting stopper. Finally remove most of the ether by heating the tube cautiously in warm water (*Caution:* no flames near) and cool. Now cautiously add a few drops of alcohol. What do you observe?

Notes

1. This is usually called the Beilstein copper oxide test.
2. The test depends on the formation of a volatile copper compound. Some organic acids, especially those containing sulfur, give weak positive tests.
3. The iodine acts catalytically. Refer to Chapter 18.

Questions

1. What causes the green color of the flame in A?
2. What is the order of reactivity of silver nitrate with the compounds tested?
3. What reactions take place in C? Write equations.
4. Does metallic sodium react with ethyl bromide? Write equations for reactions.
5. What evidence of chemical changes in F did you observe? Write equations for the reactions.
6. Calculate ΔH for the gas-phase reaction of hydrogen bromide with an alcohol.
7. Is there a difference, calculated from bond energies, in the ΔH values of reactions of hydrogen chloride with primary, secondary, and tertiary alcohols? Why?
8. Calculate the equilibrium constants in the gas-phase and liquid-phase reactions of hydrogen bromide and ethyl alcohol.
9. Calculate the equilibrium constant in the gas-phase reaction of hydrogen bromide and ethylene.

Chapter 17

DI- AND POLYHALOGENATED PARAFFINS

Many di- and polyhalogenated compounds are important industrial products and are manufactured on a large scale, as for example methylene chloride, chloroform, carbon tetrachloride, ethylene bromide, dichloroethylene, and trichloroethylene. Some of these are prepared by direct action of a halogen on a hydrocarbon. From the standpoint of value in synthetic work, the most useful compounds are those in which the halogen atoms are attached to different saturated carbon atoms. Among the most important of these are compounds with adjacently substituted carbon atoms, namely, alkene dihalides, $C_nH_{2n}X_2$.

A general method for the preparation of alkene dihalides (also of alkyne tetrahalides) consists in the direct addition of the halogen to the unsaturated hydrocarbon, as carried out in Experiment 17–1, the preparation of 2,3-Dibromobutane:

$$CH_3CH{=}CHCH_3 + Br_2 \rightarrow CH_3CHBrCHBrCH_3$$
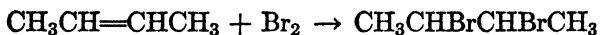
Sometimes a solvent is added, but this is not necessary if proper control is used, as in Experiment 17–1 (see also Experiment 14–1, the Preparation of Ethylene Bromide).

17.11 Thermochemistry. It is evident from simple calculations with bond-energy values that the gas-phase addition reaction of bromine or chlorine to a typical olefin is decidedly exothermic (Table 14–1). The reaction of chlorine is the more strongly exothermic. In the bromine and chlorine reactions $-\Delta H$ is so large that $-\Delta F$ likewise is quite large (see 1.43). The equilibria therefore lie so far on the side of the halogen compounds that a rise in temperature does not bring about dehalogenation. Before that happens, the reaction of dehydrohalogenation sets in.

The reaction of gaseous iodine with a typical gaseous olefin is but moderately exothermic, for ΔH is only -13.4 kcal. per mole. It is interesting that the value of the $T\Delta S$ term (Equation 1–29) for this change must be -15 kcal., since ΔF is $+2.0$ kcal. Actually the equilibrium here is a measurable one, for the equilibrium constant is 0.035 at $30°$, and 0.008 at $50°$. In this reaction, therefore, the equilibrium

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at room temperature lies on the side of the reactants. Dehalogenation is favored even more by a rise in temperature.

17.12   Reaction Rate. Liquid olefins usually react quite rapidly with chlorine or bromine, as in Experiment 17–1, where liquid 2-butene reacts with bromine. The rate of reaction of ethylene with bromine, however, is not nearly so rapid (Experiment 14–1), because: (1) Ethylene has a low solubility in liquid bromine; (2) bromine in excess is an anti-catalyst for its addition to olefins; and (3) ethylene in general reacts less readily than do higher olefins. Propylene reacts more rapidly than ethylene. Ethylene reacts slowly with iodine in alcohol. Solid ethylene iodide slowly precipitates from the solution. In this case the reaction proceeds essentially to completion, owing to the insolubility of the product (see 1.25).

17.13   Side Reactions. The principal side reaction is one of substitution, which decreases in importance in the order: chlorination > bromination ≫ iodination. Substitution by iodine is not observed usually. The substitution reaction may be: (1) independent and concurrent, or (2) dependent and "coupled" with the addition reaction. The independent reaction is observed mainly when the halogen is in excess. The tendency for chlorine to react by substitution increases with a rise in temperature or with an increase in the number of methyl groups attached to the unsaturated carbon atoms. Thus propylene yields largely allyl chloride at about 300° in the presence of oxygen, which aids by suppressing the addition reaction, whereas trimethylethylene and tetramethylethylene give largely substitution products, even at 0°.

The coupled reaction is more prominent when the olefin is in excess and is explained as a reaction of intermediate free halogen radicals (halogen atoms) with the olefin. Apparently they attack the hydrogen atoms of the olefin more readily than those of the halogenated product. The first product of the coupled reaction is a monohalogenated alkene. Since this is unsaturated, further reaction with the halogen is possible, thus forming some trihaloalkane. This substitution reaction can be minimized by: (1) keeping the halogen in excess, (2) keeping illumination low, (3) lowering the temperature, and (4) keeping the concentration of alkene low. Vigorous agitation is desirable.

17.14   Recovery and Purification. This is a comparatively simple matter, for the boiling-point separation between a dihalogenated and a higher halogenated hydrocarbon usually is fairly large. However, since polyhalogenated hydrocarbons sometimes decompose when distilled at atmospheric pressure, distillation at reduced pressure often is desirable. Bromides are more liable to decompose than chlorides.

Experiment 17-1   General Method of Preparing
Olefin Dibromides

2,3-Dibromobutane (Note 1)

Equip a 1-liter four-necked flask (Note 2) with a sealed mechanical glass stirrer, a Dry Ice reflux condenser (Figure 7-2, *I*; Note 3), a dropping funnel, and an inlet tube. The stirrer should extend nearly to the bottom of the flask and the inlet tubes about two thirds of the way down. Attach a guard tube of calcium chloride at the exit of the condenser. Surround the flask with a cooling bath at $-15°$ to $-20°$ (Note 4) of sufficient capacity to maintain a temperature of $-5°$ at the end of the experiment (Note 5). Set the whole apparatus well above the desk top so that the cooling bath can be removed easily (Note 6).

Open a *weighed* ampoule containing about 1 mole of 2-butene (Note 7), after having cooled it to the temperature at which it was sealed. Save any pieces of glass. Attach it, while still in the cooling bath, to the inlet tube of the flask. Keep the length of rubber tubing as short as possible, since rubber sometimes is permeable to butene. Support the ampoule so that the bath can be lowered gradually, and finally removed completely, thus allowing the butene to evaporate at any desired rate. Place in the dropping funnel a slight excess of dry bromine. After a small amount of butene has condensed, set the stirrer in gentle motion, and allow bromine to drop in slowly until there is a slight excess, as shown by the color of the condensed liquid. Regulate the rates of flow of butene and bromine so that bromine is in slight excess at all times (Notes 8 and 9), and increase the rate of stirring to facilitate cooling. Carry out the operation as fast as consistent with control. Decrease the rates of flow in case much hydrogen bromide is evolved (Note 10). Continue until all butene has evaporated, applying heat with the hand, but not with a flame, at the last. Add more bromine, if necessary. Determine the weights of butene and bromine used.

Shake the liquid in a separatory funnel two or three times with water to remove most of the acid present, using two separatory funnels for convenience (refer to 6.17). Remove any halogen and all remaining acid with dilute aqueous sodium carbonate (refer to 6.13 and 6.16), and wash finally with water to remove sodium carbonate. Shake the organic phase with a small amount of suitable drying agent (potassium carbonate or calcium chloride) so as to dry in stages (refer to 12.26), removing the aqueous phase, and repeating. If the liquid must stand for a time, run it into a small conical flask, and add a little more of the drying

agent. Let stand until water is well removed (refer to 12.26). Remove the drying agent by proper filtration (refer to 12.28) into a dry distilling flask of suitable size (refer to 7.11) attached to a small dry water-cooled condenser. The liquid should be perfectly clear (Note 11).

Distil slowly with a *small* flame, so as to distil over completely at the beginning any water remaining, thus completely drying the main portion of the product (refer to 12.12). Collect separately in a small flask the first, cloudy distillate. Stop when the distilling temperature is constant and/or water no longer comes over. Remove water from the distillate and also from the cooler part of the distilling apparatus where it has condensed. Add the dried distillate to the main portion, and then continue with the distillation, which should be fairly rapid in case decomposition takes place.

Collect the product as soon as it comes over at a fairly constant temperature. Collect over a 7° range, which should include the boiling point of 2,3-dibromobutane (Note 12). Calculate the percentage yield from both the olefin and the halogen. Label the product, showing name, boiling range, weight in grams, percentage yield, date, and name of student. Complete the write-up of the experiment, and report to the instructor.

Notes

1. Some other olefin may replace 2-butene. With ethylene or propylene the reaction vessel may be cooled with a mixture of Dry Ice and a suitable liquid (isopropyl ether). However, it is important to note the melting point of the desired product.

When the olefin is a liquid, the Dry Ice condenser is replaced by a water-cooled condenser, or, in the case of a higher olefin, for example heptene or a still higher olefin, the condenser may be dispensed with entirely. A calcium chloride guard tube is attached at the opening to air; otherwise, when the cooling bath is applied, moisture enters with the air. If a three-necked flask must be used, the dropping funnel can be fitted to the top of the condenser by a two-holed stopper, one hole for the funnel and the other for the guard tube.

Usually ice and water make a satisfactory cooling bath when the stirring is vigorous, since then the liquid comes in contact with a large cooling surface. However, the colder the bath, the more rapidly the reactants can be added without danger of side reactions becoming important. If the bath vessel has a capacity about 2 liters greater than that of the flask, one charge of ice usually is sufficient (refer to Question 11).

Chlorine may replace bromine. It is introduced through a glass tube, and should be passed through a wash bottle of concentrated sulfuric acid. *Caution:* The chlorine should be in only slight excess at all times. If in large excess, or if bright light enters the flask, carbon may be formed, as a result of the reaction becoming too vigorous. It is essential that the cooling be efficient and that illumination be by diffused daylight or by artificial light.

2. If a three-necked flask must be used, the reflux condenser and inlet tube can be attached to the same neck by means of a wide Y tube (addition tube). Manual shaking can replace mechanical stirring. In this case the shaking must be continuous.

3. A condenser cooled with brine at −15° or lower also is satisfactory but is not so easily manipulated   (Refer to 15.17 regarding sealed mechanical stirrers.)

4. A freezing mixture of ice and concentrated hydrochloric acid is more convenient than one of salt and gives a lower temperature (about −20°). If the acid is first chilled to about 5°, a temperature of −25° can be obtained.

5. A glass jar is preferred, in order that the color of the liquid in the flask can be observed. The volume of the cooling bath, that is, the ice and liquid, should be at least three to five times the capacity of the flask.

6. It may be necessary to examine the contents of the flask more closely or to replace the freezing mixture with a still colder one. This will be necessary if the cooling bath does not have sufficient capacity.

7. If prepared according to Experiment 14–2, this is a mixture of *cis*-2-butene and *trans*-2-butene.

8. Refer to the discussion on side reactions.

9. A small section of the ice on the outside of the vessel can be made reasonably transparent by applying a thin film of glycerol from time to time.

10. See discussion regarding the coupled reaction of substitution.

11. Usually the liquid is clear if drying is done by stages with small amounts of potassium carbonate. With larger amounts, solid is more likely to remain in suspension. This also is more likely if calcium chloride is used in place of potassium carbonate. Suspended solid is undesirable, for usually it catalyzes the splitting out of hydrogen bromide at the boiling point. Thus, use an ebullition tube rather than boiling chips during the distillation.

12. Each isomeric 2-butene yields a dibromide; that from *cis*-2-butene boils at 161°, and that from *trans*-2-butene at 158°. Since some decomposition accompanies distillation at atmospheric pressure, the operation must be carried out rapidly. Better yet, the dibromide should be distilled at reduced pressure. At 50 mm. the respective boiling points are 76° and 73°, at which temperatures the compounds are stable. The dibromide from *cis*-2-pentene boils at 94° (50 mm.), and that from *trans*-2-pentene at 91° (50 mm.). Boiling temperatures at other pressures may be read from Figure 8–2 (see also discussion on Vacuum Distillation, Chapter 8). Naturally, the higher the boiling point of a dibromide, the more likely is decomposition. Yield, 90%.

Questions

1. Why is it desirable that the freezing bath be as low as −15°?

2. Why is it desirable that the volume of the freezing bath be three to five times the capacity of the flask?

3. Why not open the butene-containing ampoule at room temperature?

4. Why not bubble butene through bromine?

5. Why keep the bromine in slight excess?

6. Why is the crude dibromobutane shaken with sodium carbonate solution?

7. What else could be used?

8. What organic compound may be formed if hydrogen bromide is eliminated during the distillation process?

9. Write equations for other methods of preparing compounds of the formula $C_4H_8Br_2$.

10. How many structurally isomeric dibromobutanes, derived from n-butane, are possible? from isobutane?

11. How much ice is melted by the reaction of 1 mole of gaseous butene with 1 mole of liquid bromine?

12. Which of two alcoholic solutions, each containing 0.01 mole of ethylene and 0.01 mole of iodine will have more ethylene iodide, one in 1 liter or one in 2 liters of alcohol, after equilibrium is reached? Which will be darker in color?

THE GRIGNARD REAGENT

The Grignard reagent is one of the most important reagents in organic chemistry because it undergoes a wide variety of synthetically useful reactions and is easy to prepare. In this chapter are discussed the preparation of the Grignard reagent and its use in the synthesis of 1-alkenes. The reactions by which alcohols are prepared are discussed in Chapter 19.

SECTION 18.1 PREPARATION OF GRIGNARD REAGENTS

Grignard reagents are prepared by the action of alkyl halides (also aryl halides in the aromatic series) on metallic magnesium in the presence of **absolute ether** (ether free of alcohol and water). In the case of n-butylmagnesium bromide (Experiment 18–1) the reaction is:

$$CH_3CH_2CH_2CH_2Br + Mg \rightarrow CH_3CH_2CH_2CH_2MgBr$$
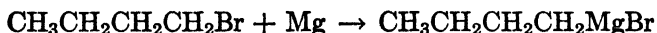
Other alkyl halides RX react similarly. The ether is not shown in the equation but is one of the reactive substances. As the reaction proceeds, the magnesium dissolves, for the alkylmagnesium halide is ether-soluble. If the ether is evaporated, the alkylmagnesium halide remains behind in the form of a solid addition compound with ether, $RMgX \cdot (C_2H_5)_2O$ or $RMgX \cdot 2(C_2H_5)_2O$. The existence of such compounds explains the ready solubility of the alkylmagnesium halide in ether. It is not necessary to isolate the solid Grignard reagent, for all subsequent reactions may be carried out with the ether solution.

18.11 Rates. The rate with which properly prepared magnesium reacts with an alkyl halide in the presence of absolute ethyl ether (or a higher ether, or a tertiary amine) and during vigorous stirring usually is satisfactory at the boiling point of ethyl ether but may not be satisfactory at a lower temperature. The ability of ether to form a coordination complex with the alkylmagnesium halide probably explains its value in this reaction. The reaction sometimes will proceed in the absence of ether at elevated temperatures. In butyl ether the reaction is slower than in ethyl ether at similar conditions, but, since the tempera-

ture may be raised above the boiling point of ethyl ether, the reaction rate can be increased. Butyl ether is preferred if the desired product has a low boiling point, as in the preparation of the lower 1-alkenes (Experiment 18–2).

Moisture and alcohols hinder the reaction. In ordinary ethyl ether, which contains both water and alcohol, no reaction takes place. The concentration of these must be quite low before a satisfactory rate is realized. Even when the best grade of ether is used, the reaction often does not take place at first, because the ether, when being transferred from one vessel to another, picks up water, either from moist air with which it has come in contact, or from the walls of vessels which usually have a film of water. For these reasons absolute ether for this reaction should come in contact only with glass vessels which have been thoroughly dried (at 110°), and it should be transferred by either distillation or siphoning. Once the reaction has started, it proceeds usually without difficulty because no moisture or alcohol can be present.

Ethyl ether, essentially free of water and alcohol, can be obtained by thoroughly mixing ordinary ether with about one-fourth the volume of cold concentrated sulfuric acid (*Caution:* cooling) and then at once distilling the ether as rapidly as possible through a very long condenser. If this is done slowly the recovery is low, owing to the reaction of sulfuric acid with ether. Usually ether so purified is satisfactory, but as an added precaution it should stand overnight with some metallic sodium. A less satisfactory method consists of shaking ordinary ether with aqueous calcium chloride, stirring with anhydrous calcium chloride, and distilling. This second method must be supplemented by standing over metallic sodium (wire) and redistilling. The so-obtained absolute ether is stored over metallic sodium, preferably in wire form. For removing water and butyl alcohol from butyl ether, distillation usually is sufficient (Section 9.2, and Experiment 22–2, Note 4).

The amount of ether must not be too small. Part of the solvent enters into combination with the alkylmagnesium halide. This should be kept in solution by having a sufficiently large volume of solvent. The reaction is started with a small amount of ether (see the following), and the remainder of the solvent is introduced along with the alkyl halide, three or more volumes of ether per one of alkyl halide.

The magnesium should have a large surface and should be essentially free of magnesium oxide and water. The magnesium may be in the form of ribbon or turnings. Usually in ribbon form the surface is covered with a firmly adhering layer of oxide, which hinders reaction. This can be removed by scraping. However, a more satisfactory form consists of the turnings from a bar of magnesium metal, as obtained with a

lathe. These should be turned just before use, washed with ether to remove the film of oil, and quickly dried in an oven. They should be placed in an oven-dried bottle until needed.

Stirring is necessary since the system is heterogeneous, and it *should be as vigorous as possible*. In those cases where the alkyl halide itself reacts (couples) with the Grignard reagent (tertiary butyl chloride or allyl bromide), violent agitation is absolutely necessary if a good yield of the reagent is desired.

18.12   Starting the Reaction. Usually the reaction will start if the initial concentration of the alkyl halide in ether is high or if a suitable catalyst is present. A few milliliters each of the alkyl halide and ether are added to the magnesium in the flask, and heat is applied gently. Reaction should start in a few minutes, as shown by the development of heat, the formation of a slight cloudiness in the liquid, and/or the disappearance of some of the magnesium. If none of these happens, it is desirable to add a *small* amount of catalyst, for example dry iodine, or a mixture of magnesium and iodine which has been heated to a red heat in a test tube. In each of these cases the actual catalyst is believed to be magnesious iodide MgI. This is a highly reactive compound, very soluble in ether. After the reaction has once started, but not before, the main reaction mixture can be added. Further reaction should proceed without any difficulty. The advantages of this procedure are: (1) a high initial concentration of the alkyl halide, (2) a higher reaction temperature initially, (3) easy control in preparing the first small portion of reagent, and (4) removal, by this portion of reagent, of traces of impurities in the bulk of the ether, which might hinder the reaction. Sometimes, when the alkyl halide has a high molecular weight, the reaction is so difficult to start that it is desirable to add a small amount of an easily prepared Grignard reagent, for example methylmagnesium iodide.

18.13   Thermochemistry. The formation of the Grignard reagent from the alkyl halide and metallic magnesium is a strongly exothermic reaction. Therefore, reaction runs essentially to completion. Care must be taken that the reaction does not get out of control. Control is possible by cooling and/or by regulating the rate of addition of the alkyl halide. In general, when ethyl ether is the solvent, the student is faced with the necessity of removing a rather large amount of heat without allowing the temperature to drop much below the boiling point (see 1.31, page 16; also 7.23, Refluxing). This is best accomplished by means of vigorous agitation and by the use of a liquid bath a little below the temperature of boiling ether (35°). It is desirable that the ether keep refluxing from the condenser for then: (1) The temperature is a

maximum, and (2) the alkyl halide is known to be reacting. It is important that the concentration of the alkyl halide be kept low. One can be sure that the reaction is progressing smoothly by removing the cooling bath from time to time as the alkyl halide is being run in and noting the effect on the rate of reflux.

18.14   Side Reactions.   Side reactions which diminish the yield of Grignard reagent are (1) coupling, (2) unsaturation, (3) reaction with carbon dioxide, (4) oxidation. The coupling reaction to form the hydrocarbon R–R is exceedingly slow when R is a lower primary radical but may be fairly rapid when R is large or when it is a tertiary radical, or when it is of the allyl type; that is, $RCH{=}CHCH_2X$ (or the benzyl type). The coupling reaction may be minimized by: (1) violent agitation, (2) high dilution of the Grignard reagent, (3) excess of magnesium, and (4) use of alkyl chlorides, especially in the case of secondary and tertiary alkyl halides.

Unsaturation may be fairly extensive in the case of tertiary halides, less so with secondary. Iodides unsaturate the most easily. Access of air to the mixture allows it to react with carbon dioxide and oxygen, producing an acid and an alcohol, respectively. Ordinarily air has little access, so long as the temperature of the reaction mixture does not fluctuate markedly. Alternation of heating and cooling causes air to flow up and down the condenser, whereas otherwise air enters only slowly by diffusion.

18.15   Determination of Grignard Reagent.   The concentration of Grignard reagent in a solution can be determined by decomposing a sample with water or alcohol and titrating the base that is formed (see Experiment 18–3). Analysis is recommended in general and should be made whenever side reactions are prominent.

SECTION 18.2   REACTIONS OF GRIGNARD REAGENTS

The Grignard reagent is useful in a large number of syntheses. Those discussed in this laboratory manual are (*a*) alkanes, Chapter 13; (*b*) 1-alkenes, Chapter 14; (*c*) alcohols, Chapter 19; (*d*) acids, Chapter 20; and (*e*) ketones, Chapter 25.

(*a*) $H_2O + C_4H_9MgBr \rightarrow C_4H_{10} + MgBrOH$

(*b*) $CH_2{=}CHCH_2Br + C_4H_9MgBr \rightarrow CH_2{=}CHCH_2C_4H_9 + MgBr_2$

(*c*) $CH_3CHO + C_4H_9MgBr \rightarrow CH_3CH(OMgBr)C_4H_9$

$H_2O + CH_3CH(OMgBr)C_4H_9 \rightarrow$

$CH_3CH(OH)C_4H_9 + MgBrOH$

(d) $CO_2 + C_4H_9MgBr \rightarrow C_4H_9CO—OMgBr$

$H_2SO_4 + C_4H_9CO—OMgBr \rightarrow C_4H_9COOH + MgBrHSO_4$

(e) $CH_3COCl + C_4H_9MgBr \rightarrow CH_3COC_4H_9 + MgBrCl$
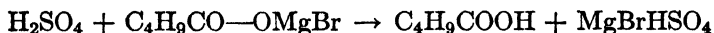
18.21 Heat Effects in Reactions of Grignard Reagents. Large heat effects are characteristic of many reactions of Grignard reagents, especially with water and alcohols (a), aldehydes, ketones, esters, etc., (c), carbon dioxide (d), and acid halides (e). Also much heat is given off when water is added to the magnesium salt resulting from the action of the Grignard reagent on another compound, such as in b, c, d, and e. For example, the heat of hydration of anhydrous magnesium chloride is 33 kcal. and of anhydrous magnesium sulfate 23 kcal. per mole. In general the reactions proceed very rapidly, not only at room temperature but also at 0°. In order to carry them out with even moderate rapidity and under good control, an efficient cooling bath of good capacity is essential. The heat effect is so pronounced that, when a drop of water or of alcohol is added to the Grignard reagent in ethyl ether, vigorous boiling takes place locally. This may be violent enough to cause ether to spurt out of the condenser. Control is easy if a dilute solution of water in ether (ethyl) is used.

18.22 Side Reactions. The reagent sometimes is used in the reaction vessel in contact with unreacted metallic magnesium in case there is no subsequent reaction. However, in general it is preferable to transfer the solution by means of a siphon to a second dry flask. The pinacol reaction may result from the action of metallic magnesium on some ketones and some unsaturated aldehydes. Saturated aldehydes are not affected.

18.23 Recovery of Reaction Products. When a hydrocarbon is being prepared as in a or b, it can be distilled directly from the reaction mixture, if volatile enough. If, however, the solvent must be distilled away from the product, then it is necessary to remove completely magnesium salts with water.

The precipitate of magnesium hydroxide which results from the action of water in a and c must be dissolved by the addition of an aqueous solution of an acid, for example sulfuric acid, or of an ammonium salt, for example ammonium chloride, in order to be able to separate the two liquid phases. Here again the reaction is rapid, and heat is evolved. A disadvantage in the use of sulfuric acid is the catalytic effect of traces of acid, in case it is not *completely* removed from the ether solution, causing decomposition of an alcohol during the distillation. A disadvantage in the use of an ammonium salt is the slow precipitation of mag-

nesium carbonate on exposure to air, sometimes producing an emulsion which interferes with separation.

Experiment 18-1 illustrates the general preparation of a Grignard reagent, in this case *n*-butylmagnesium bromide. A little of the Grignard reagent is used in Experiment 18-3, The Properties of Grignard Reagent. The rest may be used in Experiment 18-2, The General Method of Preparing 1-Alkenes, or in Experiment 19-4, The General Method of Preparing Alcohols.

Experiment 18-1   General Method of Preparing Grignard Reagents (Notes 1 and 2)

n-Butylmagnesium Bromide

To 400 or 500 ml. of *absolute* ethyl ether (*Caution:* Note 3) in a dry 1-liter flask add some metallic sodium (wire or fine shavings, Notes 3 and 4), and let stand, with occasional agitation while the apparatus is being assembled. The evolution of hydrogen should slacken and be insignificant in an hour or so. Protect with a guard tube containing anhydrous calcium chloride in case the ether must stand for some time (Note 5).

Provide a dry 1-liter three-necked flask (Note 6) with a sealed mechanical stirrer (Note 7), a dry efficient reflux condenser, and a dry dropping (or separatory) funnel, arranged so as to deliver the entering liquid onto an actively moving part of the reaction mixture. Support the flask high enough to permit a cooling bath to be moved under it from the side (Note 8). Protect the condenser and dropping funnel from the moisture of the air by guard tubes of anhydrous calcium chloride (Note 9). To the end of the guard tube on the condenser attach a long rubber tube extending almost to the floor to keep the heavy ether vapor from passing along the desk and being ignited by a burner.

Put a 20% excess of clean magnesium turnings in the flask, *ca.* 5 g. of the alkyl halide (part of the total amount specified below), *ca.* 10 ml. of anhydrous ethyl ether, and a small crystal of iodine. Allow the mixture to stand until reaction sets in, warming if necessary to 45° or 50° (Note 10). After the initial reaction has subsided, add enough anhydrous ethyl ether to permit good agitation (Note 11). Then from the dropping funnel add dropwise 1.0 mole of *n*-butyl bromide, or other alkyl halide, in case some other Grignard reagent is being prepared (Note 12), diluted with *ca.* 300 ml. of absolute ether (Notes 13 and 14). Stir violently. Ether should reflux from the condenser after a few milliliters of the alkyl halide solution has been added (Note 15).

Once ether refluxes smoothly, the alkyl halide may be added more rapidly, the reaction being kept under control by efficient refluxing or by applying some external cooling. However, do not cool the mixture too much, but keep it at the boiling point of ethyl ether (Note 16).

After all of the alkyl halide has been added, remove the cooling bath, and continue the agitation and refluxing until the reaction is finished, heating if necessary with a bath of warm water. Use some of the reaction mixture in Experiment 18–3 and the rest in Experiment 18–2 or 19–4. Calculate the percentage yield (Note 17).

Notes

1. The decision as to whether ethyl ether or butyl ether is to be the solvent is reached by considering the subsequent reactions of the Grignard reagent. For the preparation of low-boiling substances, for example 1-butene, 1-pentene, or 1-hexene, butyl ether is preferred, and for the preparation of compounds boiling above 100°, for example higher 1-alkenes, 2-pentanol, and higher alcohols, ethyl ether is preferred. For 1-heptene either ether can be used. The experiment is written for ethyl ether. Modifications to be followed for butyl ether are given in subsequent notes.

2. When butyl ether is the solvent, the condenser may be short, or it may even be dispensed with entirely if the alkyl halide is not volatile at 50° to 70°. Under these conditions it is necessary that the temperature be controlled properly. Therefore a thermometer must extend into the reaction mixture.

3. *Caution* in use of ether and metallic sodium: Observe precautions given in Preparation of 2-Pentene (Experiment 14–3) in regard to inflammable liquids, and keep vessels away from flames. Read Experiment 15–1 Note 10, in regard to handling metallic sodium.

4. In case no absolute ethyl ether (free of both water and alcohol) is available, mix ordinary ether (700 ml.) with one-fourth its volume of concentrated sulfuric acid, adding the sulfuric acid slowly to the ether with constant agitation and *thorough* mixing (preferably in a large flask) while cooling in an ice bath or in a stream of water from the tap. Distil the ether, heating with a hot water or steam bath, through a long (90-cm.) condenser with the proper precaution (see Note 3). Ether so obtained should stand overnight with metallic sodium. Decant from any flocculent precipitate.

5. Butyl ether which distils close to 141° is essentially anhydrous and free of butyl alcohol. Test the material by distilling some *slowly*.

6. Draw dry air through the flask while it is being heated. This may be done after the apparatus is assembled. Be sure that the flask is cold before adding ethyl ether.

7. Refer to Subsection 15.17.

8. The bath can be supported on a low stand or on blocks of wood.

9. Each should be attached by means of a short glass bend so that, in case the calcium chloride liquefies, it cannot run into the apparatus.

10. When butyl ether is the solvent, it may be necessary to heat to about 70°.

11. Preferably this should be allowed to run in from the dropping funnel (*Caution* regarding flames with ethyl ether). Oftentimes, especially when the ether contains

water or alcohol, again the reaction is slow to start. On this account, do not add any more ether than necessary (see Question 4).

12. Methyl bromide may be used, even though it is a gas.

13. The volume of the Grignard solution should be known in order for you to be able to calculate later from the titration data the amount of Grignard reagent produced.

14. When butyl ether is the solvent, the volume should be 600 to 800 ml. since it is a poorer solvent for Grignard reagents.

15. When butyl ether is the solvent, bring the temperature to 50° before adding the solution. The temperature should rise as the solution is run in and soon reach 70°. Keep at 50° to 70°, applying external cooling if necessary. At still higher temperatures side reactions may take place.

16. If the refluxing stops, remove the bath in order to ascertain whether the reaction is over or whether the mixture is too cold. If the latter, refluxing should start again shortly, with the bath removed.

17. Refer to Subsection 18.15 and Experiment 18–3.

Questions

1. What are the advantages of using butyl ether?

2. What are the advantages of using ethyl ether?

3. Why is it desirable to have the first portion (5 ml.) of butyl bromide react before more is added?

4. How much water can be present in the ether that is added to cover the magnesium, without preventing subsequent reaction, assuming that all of the initial alkyl halide is converted to the Grignard reagent (Note 11)?

5. Explain how iodine aids the reaction.

6. Which reagent is in excess, and why?

7. Why is ethyl ether a better solvent than n-butyl ether for n-butylmagnesium bromide?

8. Explain how, in the preparation of allylmagnesium bromide, the yield is improved by: (a) agitation; (b) dilution; (c) excess magnesium.

9. How is the yield of Grignard reagent determined?

10. What is the reaction product (or products) when to n-butylmagnesium bromide the following is added: (a) acetone; (b) allyl bromide; (c) carbon dioxide; (d) ether; (e) ethyl alcohol; (f) oxygen; (g) water?

Experiment 18–2   General Method of Preparing 1-Alkenes

1-Heptene

Separate the unreacted magnesium from the Grignard reagent of Experiment 18–1 by forcing the solution through a dry glass tube by dried compressed air (Note 1), into a dry flask provided with a reflux condenser (Note 2), a dropping funnel, and a sealed mechanical stirrer. In a test tube add about 0.5 ml. of allyl bromide to 2 or 3 ml. of the Grignard solution, and heat gently to start the reaction (Note 3). After this has reacted well, add it to the main portion of the Grignard solution, and allow allyl bromide (0.8 mole per mole of Grignard reagent, Note 4) to flow into the mixture as rapidly as consistent with temperature control. *It is important that allyl bromide react as it is added* (Note 5). Stir continuously. Remove the stirrer, and let stand overnight. Replace all rubber stoppers with cork stoppers (Note 6).

WHEN THE SOLVENT IS ETHYL ETHER. The reaction mixture separates into two liquid phases (Note 7); sometimes the lower phase solidifies. When this happens, the upper ether phase can be decanted, and this can be added later to the ether phase obtained after decomposition with water, as described in the following paragraph.

To the entire reaction mixture in ethyl ether, or to the solidified lower phase, with original equipment of stirrer, condenser, dropping funnel, and cooling bath, add about 200 ml. of water from the dropping funnel, at first dropping the water cautiously near the stirrer and then later adding it as rapidly as consistent with temperature control (Note 8), and with violent agitation and cooling by an ice-water or ice-salt bath. Then with agitation and cooling add aqueous ammonium sulfate or cold dilute sulfuric acid until the precipitate of magnesium hydroxide has dissolved (Note 9). Separate the two layers in a large separatory funnel (*Caution:* Turn out flames near by). Remove magnesium salts and any sulfuric acid by several washings with water. If the ether solution tests acid to moist neutral litmus paper, repeat with aqueous sodium carbonate or sodium hydroxide. Dry the ether solution with anhydrous potassium carbonate, anhydrous magnesium sulfate, or anhydrous calcium chloride, letting stand overnight in a large conical flask (Note 10). However, if potassium carbonate is used, first remove most of the water in stages by shaking the ether solution with *small* portions of the drying agent, drawing off the aqueous phase that forms (Note 11). Filter if not clear (*Caution:* flames).

Strip off the ethyl ether by distillation through a packed fractionating column, not less than 20 cm. long, and provided with a reflux condenser. Heat with a small (micro-) flame. Condense the ether with a long

(90-cm.) condenser, and take the usual precautions with volatile solvents (Note 12).   If one is available, use a two-necked flask large enough to hold conveniently the expected amount of product and having a packed column in the neck (Figure 9–4, *G*).   With this, run the solution in as the solvent is distilled.   As soon as the distilling temperature rises above that of pure ether, start making cuts.   Continue until the temperature approaches that of 1-heptene.   Transfer the heptene to a small flask for storage.   Rinse the column and flask with 5 or 10 ml. of ether, transfer the rinsings to a small distilling flask, and slowly distil out ether with a microflame.   Following the procedure of systematic fractionation (Note 13), add the cuts, and distil as before.   Finally add the main heptene fraction, and distil slowly through a small condenser, heating with a microflame.   Collect the product over a 5° range near the boiling point of heptene.

WHEN THE SOLVENT IS BUTYL ETHER.   Apply heat directly to the reaction mixture by means of an oil bath.   Distil through a short wide tube until only butyl ether distils (Note 14).   Purify by slow distillation, using a microburner, a small distilling flask, and a small condenser. Take cuts below and above the boiling point of heptene, and refractionate in systematic fashion (Note 13).   Collect as before.   The butyl ether must not be discarded.   Recover the butyl ether by distillation, after first removing magnesium salts by thorough washing with water.

The product should be free of any organic bromide, as shown by test with alcoholic silver nitrate.   Calculate the percentage yield (Note 15). Label the product properly, showing name of compound, boiling point, percentage yield, and name of worker.

Notes

1. Use a drying tube for drying the air.

2. In case 1-butene is being prepared, a tube should lead from the top of the condenser through: (*a*) a safety device which protects against decrease of pressure and sudden increase of pressure; (*b*) a purifying train of three wash bottles containing, respectively, a solution of potassium hydroxide in 50% aqueous alcohol and two solutions of 50% (by weight) sulfuric acid; and (*c*) a drying tower of anhydrous calcium chloride.   Collect in an ampoule cooled by Dry Ice (see Experiment 14–2).   A safety tube as in Experiment 14–2 cannot be used, since the solid magnesium salt which separates may close the tube.   Calculate the pressure required to force gas through the wash bottles, and be sure that the height of mercury in the stirrer is adequate

3. The reaction is slow to start but, once started, proceeds at a satisfactory rate If the small test portion does not react, transfer it to another test tube in which have been previously heated (and cooled) a crystal of iodine and a small amount of magnesium turnings.   Warm gently until reaction starts.

4. With an excess of Grignard reagent, the allyl bromide will react completely, given sufficient time.

5. If ethyl ether is the solvent, it should soon boil. If butyl ether is the solvent, heat first to about 60°. The heat of reaction should keep the ethyl ether boiling or cause the temperature of the butyl ether to rise. Maintain the butyl ether at 50° to 70°. External cooling may be employed so that allyl bromide may be added at a reasonably rapid rate.

6. Rubber stoppers sometimes become so swollen, on account of absorbed solvent, that reinsertion in the flask is not possible, after they have been removed.

7. The upper phase is composed mainly of ethyl ether and heptene; the lower phase is composed mainly of ether and magnesium bromide.

8. If the water is added slowly, the flask soon becomes filled with a solid mass which cannot be stirred effectively. However, if the stirring is vigorous enough to keep the mixture in violent agitation, and if the cooling is effective, it is possible to add the water so rapidly that decomposition is complete before the solid clumps together.

9. To avoid a needlessly large excess, take a 5 or 10% excess of the calculated amount.

10. Refer to 12.27, Speed of Drying.

11. Refer to 12.28, Removal of Drying Agent.

12. Refer to Experiment 14–3, The Preparation of 2-Pentene.

13. Refer to discussion in 9.13 on fractionation by cuts.

14. In case 1-pentene is being prepared in butyl ether, it may be allowed to distil out as formed. However, it is then more liable to contain allyl bromide.

15. Yields are 70 to 75%.

Questions

1. Why should the magnesium metal be removed before the experiment is started?

2. What are the advantages of butyl ether as the solvent?

3. What are the advantages of ethyl ether as the solvent?

4. Which reagent is in excess and why?

5. Why is it important that the allyl bromide react as it is added?

6. How can the completeness of the reaction be measured?

7. Why should the reaction mixture separate into two liquid phases?

8. What is the precipitate in the mixture after decomposition with water?

9. In case 1-butene is being prepared, explain the purpose of the three wash bottles.

10. Which drying agent is best for drying an ether solution of 1-heptene?

11. When removing ethyl ether why is a fractionating column desirable?

12. What are the probable impurities in the product, and how can they be removed?

13. What per cent of the product you obtained would have been lost if the distillation had been made from a 1-liter flask?

14. Show how to calculate ΔH for the over-all reaction when ethane (gas) is made from ethyl bromide (liquid) by first forming the Grignard reagent, which is subsequently decomposed by dilute aqueous hydrobromic acid. Make one calculation with only two ΔH values of formation from the elements, namely, -167.3 and -28.6 kcal., which are, respectively, ΔHf of $MgBr_2$ and HBr in dilute aqueous solution. Additional data can be obtained from bond energies (Table 1–1) and from heats of vaporization (Table 8–1) or Trouton's rule (Equation 8–4). State what assumptions if any are made.

Experiment 18-3   Properties of Grignard Reagent

A QUANTITATIVE DETERMINATION. Pipette accurately 5 ml. of the Grignard reagent into a 200-ml. Erlenmeyer flask. Recall Experiment 6–1, Note 3. Add 50 ml. of water dropwise at first, with vigorous shaking. Titrate with 0.25 N hydrochloric acid, using methyl red (Note 1) as the indicator. Calculate the yield of Grignard reagent in Experiment 18–1.

B REACTION WITH ALCOHOL. Add 2 to 5 drops of alcohol to 1 to 2 ml. of Grignard reagent.

C REACTION WITH CARBON DIOXIDE. To 4 to 5 ml. of Grignard reagent add a piece of Dry Ice which weighs 2 or 3 g., and which has been wiped free from moisture. Add dilute sulfuric acid to the mixture until there is an excess, as shown by a pH of 3 or less (Note 2). Note if there is a change in odor.

D IDENTIFICATION. Heat for a few minutes in a water bath with frequent shakings a mixture of 3 ml. of Grignard reagent and 1 g. of mercuric bromide (Note 3). Evaporate to dryness. Boil the residue with 8 to 10 ml. of 95% alcohol, and filter. Add 4 to 5 ml. of water to the filtrate, and cool in ice (Note 4). Collect the solid on a small Hirsch funnel by suction filtration. Determine the melting point. Recrystallize until a constant-melting point is reached, by dissolving in 95% alcohol and adding water to 60 or 65%.

E QUALITATIVE TEST. To 0.5 ml. of a 1% solution of Michler's ketone (p, p'-bis-dimethylaminobenzophenone) in benzene, add 0.5 ml. of the Grignard reagent. Add 1 ml. of water and several drops of 0.01 M iodine in glacial acetic acid, and shake (Note 5).

Notes

1. The titration can be carried out more rapidly and more accurately if an excess of standard acid is added and the excess back-titrated.

2. Use universal indicator paper or Congo red paper. The latter is blue when the pH is 3.

3. The compound in the case of n-butylmagnesium bromide is n-butyl mercuric bromide C_4H_9HgBr.

4. The compound dissolves well in 95% alcohol and separates from 60 to 70% alcohol by volume.

5. The greenish-blue color results from the formation of a dye of the diphenyl-methane type:

$$p\text{-Me}_2\text{NC}_6\text{H}_4 \!\!\!\diagdown$$
$$\text{C=O} + \text{RMgX} \rightarrow$$
$$p\text{-Me}_2\text{NC}_6\text{H}_4 \!\!\!\diagup$$

$$\begin{array}{c} p\text{-Me}_2\text{NC}_6\text{H}_4 \diagdown \quad \diagup \text{OMgX} \\ \text{C} \\ p\text{-Me}_2\text{NC}_6\text{H}_4 \diagup \quad \diagdown \text{R} \end{array} \xrightarrow{\text{H}^+}$$

$$p\text{-Me}_2\text{N}^+\!\!=\!\text{C}_6\text{H}_4\!\!=\!\!\underset{\underset{\displaystyle \text{R}}{|}}{\text{C}}\!\!-\!\!\text{C}_6\text{H}_4\!\!-\!\!\text{NMe}_2$$

greenish-blue dye cation
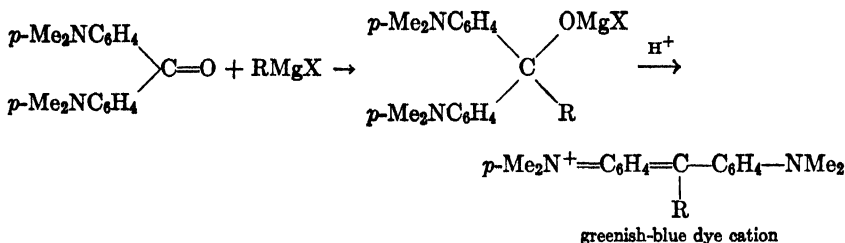
With the ethyl Grignard, which is the least sensitive of the Grignard reagents, the color develops in solutions stronger than 0.04 M. In the absence of iodine the color fades.

Questions

1. What are the reactions taking place in A, B, C, and D?

2. Why is methyl red used as the indicator in A?

3. What property of the product in C indicates the formation of another compound? What is it?

4. Of what value is a reaction such as D where solid derivatives of most alkyl halides can be formed easily?

Chapter 19

ALCOHOLS

Alcohols are important from a synthetic standpoint as they are the usual starting materials in aliphatic syntheses. Not only are they easily convertible into alkenes (Chapter 14) and into alkyl halides (Chapter 16), but by oxidation methods other types of compounds can be obtained, namely, acids (Chapter 20) and aldehydes and ketones (Chapter 25).

In industry many alcohols are produced in large quantities: methanol, by hydrogenation of carbon monoxide; ethyl, n-butyl, and isoamyl alcohols by fermentation processes; isopropyl, sec-butyl, and $tert$-butyl alcohols by hydration of olefins; pentanols from the pentyl chlorides; and higher alcohols, for example lauryl alcohol, by the hydrogenolysis of fats.

General methods of preparing alcohols are: (a) hydration of olefins, (b) hydrolysis of alkyl halides, (c) hydrolysis of esters, (d) reaction of Grignard reagents, (e) hydrogenation of aldehydes and ketones, (f) hydrogenolysis of esters, (g) reduction of aldehydes and ketones by aluminum isopropoxide; (h) reduction of aldehydes, ketones, and esters in other ways. β-Chlorinated alcohols are prepared by (i) the addition of hypochlorous acid to olefins.

(a) $\quad CH_3(CH_2)_2CH{=}CH_2 + H_2O \xrightarrow{H_2SO_4} CH_3(CH_2)_2CHOHCH_3$

(b) $\quad\quad\quad\quad C_5H_{11}Cl + H_2O \longrightarrow C_5H_{11}OH + HCl$

$\quad\quad\quad\quad\quad C_2H_5I + H_2O \longrightarrow C_2H_5OH + HI$

(c) $\quad\quad CH_3COOC_2H_5 + H_2O \longrightarrow C_2H_5OH + CH_3COOH$

(d) $\quad CH_3CHO + C_4H_9MgX \rightarrow C_4H_9(CH_3)CHOMgX \rightarrow$

$$C_4H_9(CH_3)CHOH$$

$(CH_3)_2CO + C_4H_9MgX \rightarrow C_4H_9(CH_3)_2COMgX \rightarrow$

$$C_4H_9(CH_3)_2COH$$

$H_2CO + C_4H_9MgX \rightarrow C_4H_9CH_2OMgX \rightarrow$

$$C_4H_9CH_2OH$$

$$CH_2OCH_2 + C_4H_9MgX \rightarrow C_4H_9CH_2CH_2OMgX \rightarrow$$
$$C_4H_9CH_2CH_2OH$$

$$CH_3CO_2C_2H_5 + C_4H_9MgX \rightarrow (C_4H_9)_2CH_3COMgX \rightarrow$$
$$(C_4H_9)_2CH_3COH$$

(e) $$H_2 + C_4H_9CHO \longrightarrow C_4H_9CH_2OH$$

$$H_2 + (CH_3)_2CO \longrightarrow (CH_3)_2CHOH$$

(f) $$2H_2 + C_{11}H_{23}COOR \xrightarrow[\text{catalyst}]{\text{pressure}} C_{11}H_{23}CH_2OH + ROH$$

(g) $$3C_4H_9CHO + [(CH_3)_2CHO]_3Al \rightleftharpoons$$
$$(C_4H_9CH_2O)_3Al + 3(CH_3)_2CO$$

$$(C_4H_9CH_2O)_3Al + 3(CH_3)_2CHOH \rightleftharpoons$$
$$3C_4H_9CH_2OH + [(CH_3)_2CHO]_3Al$$

(h) $$2Na + 2C_2H_5OH + C_4H_9CHO \longrightarrow$$
$$C_4H_9CH_2OH + 2C_2H_5ONa$$

$$2Na + 2C_2H_5OH + (CH_3)_2CO \longrightarrow$$
$$(CH_3)_2CHOH + 2C_2H_5ONa$$

$$4Na + 4C_2H_5OH + C_4H_9CO_2C_2H_5 \longrightarrow$$
$$C_4H_9CH_2OH + C_2H_5OH + 4C_2H_5ONa$$

(i) $$CH_3CH=CHCH_3 + HOCl \longrightarrow CH_3CHOHCHClCH_3$$

19.11   Hydration of Olefins.   Method a is the reverse of the dehydration of alcohols to olefins, which is discussed in Chapter 14. The equilibrium conditions at 25° are such that an olefin is converted into an alcohol, provided the rate is satisfactory. A "tertiary base" olefin, such as isobutylene, hydrates readily at 25° in the presence of 1 M sulfuric acid. In 15 minutes this hydrocarbon in aqueous solution is half converted into the tertiary alcohol, trimethylcarbinol. In order to convert ethylene into ethyl alcohol, it is necessary to absorb it in fuming sulfuric acid, to form ethyl hydrogen sulfate, which when heated with water is converted into ethyl alcohol:

$$CH_2=CH_2 + H_2SO_4 \rightarrow CH_3-CH_2-O-SO_2-OH$$

$$CH_3CH_2-O-SO_2-OH + H_2O \rightarrow CH_3CH_2OH + H_2SO_4$$
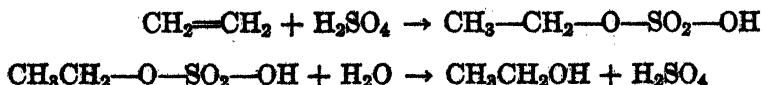
The sulfuric acid can be concentrated by evaporation. Straight-chain olefins are intermediate in reactivity between isobutylene and ethylene. Thus 2-pentene hydrates in 80% sulfuric acid at 20° (Experiment 19-3), but not in 1 M sulfuric acid. Some alkyl bisulfate is formed at the same time, and this when diluted with water and heated yields the alcohol. In this case, then, the conversion of the olefin to the alcohol proceeds *via* two paths, one direct hydration, the other through the alkyl bisulfate. The alkyl bisulfate hydrolyzes in an excess of dilute sulfuric acid more or less completely in 2 to 6 hours at room temperature and, of course, quite rapidly at 70 to 80°. The alcohol may be recovered by extraction or, more simply, by distillation. Naturally, this last should be done *rapidly* and without fractionation, to minimize the reversal of the hydration reaction.

19.12   Hydrolysis of Alkyl Halides.   Method b is the reverse of the formation of alkyl halides from alcohols. The thermochemistry is discussed in Chapter 16. Since these are equilibrium systems, and since the positions of equilibrium are not markedly different for the three classes of alcohols, the halides which are formed the most rapidly from the corresponding alcohols, as for example the tertiary alkyl halides, are the ones that hydrolyze the most rapidly. The reactions usually are carried out by means of aqueous alkali, for then the reverse reaction is eliminated. With a base present a reaction involving hydroxide ion is more rapid than one involving water, in the case of primary and secondary alkyl halides. Reaction is markedly accelerated by the presence of a small amount of sodium palmitate or other similar salt. Industrially the reaction is important with chlorides, which are obtained easily from saturated hydrocarbons by chlorination:

$$NaOH + C_5H_{11}Cl \rightarrow C_5H_{11}OH + NaCl$$
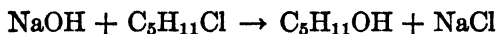
Primary chlorides react slowly at 180°. Usually the temperature is higher, up to 280°.

19.125   Hydrolysis of Esters.   In method c the reaction is catalyzed by hydronium ion, hydroxide ion, and the enzymes of the lipase type. The acid-catalyzed hydrolysis of esters is the reverse of esterification, which is discussed in Chapter 21. Since the position of equilibrium is much the same for a large variety of esters, those that form most rapidly are the ones that hydrolyze most rapidly. In industry much use is made of the Twitchell reagent for hydrolyzing fats and other esters insoluble in water. It is a strongly acidic emulsifying agent. Its value lies in its ability to act simultaneously as a catalyst and as an emulsifier.

Alkaline hydrolysis has the advantage that the reverse reaction is eliminated, as in the saponification of glyceryl palmitate.

$$3NaOH + (C_{15}H_{31}COO)_3C_3H_5 \rightarrow 3C_{15}H_{31}COONa + C_3H_5(OH)_3$$
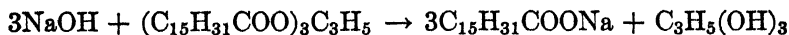
19.13 The Grignard Synthesis. Method d is the most useful method for synthesizing alcohols (see Experiment 19-4) because: (1) Grignard reagents in general are easily prepared; (2) a large number of reagents are available in the form of aldehydes, ketones, and esters; (3) the reaction of these with the Grignard reagent proceeds rapidly; and (4) the isolation and purification of the product are comparatively easy.

The preparation and utilization of the Grignard reagent are discussed in Chapter 18. It is well to recall that a primary alcohol results from the action of the reagent with formaldehyde or ethylene oxide, a secondary with any other aldehyde or with ethyl formate, and a tertiary with a ketone or with an ester other than a formate.

The preparation of 2-hexanol from n-butylmagnesium bromide and acetaldehyde (Experiment 19-4) is a typical Grignard synthesis.

$$CH_3CHO + CH_3(CH_2)_3MgBr \rightarrow CH_3CH(OMgBr)(CH_2)_3CH_3$$

$$H_2O + CH_3CH(OMgBr)(CH_2)_3CH_3 \rightarrow$$

$$CH_3CH(OH)(CH_2)_3CH_3 + BrMgOH$$

$$H_2SO_4 + BrMgOH \rightarrow BrMrgSO_4H + H_2O$$
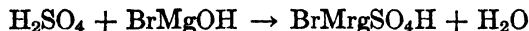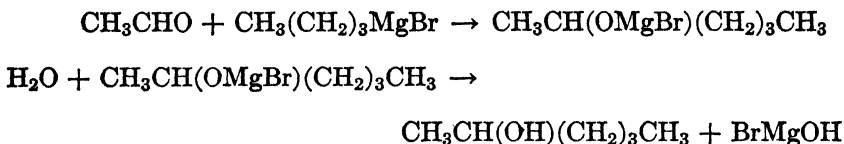
Other alcohols may be prepared by the same general procedure, using other Grignard reagents in place of n-butylmagnesium bromide, and ketones, esters, or other aldehydes in place of acetaldehyde. When ethylene oxide is used, the reaction does not take place until most of the ethyl ether has been removed, and then with great rapidity.

19.14 Hydrogenation of Aldehydes and Ketones. In method e calculation from bond-energy values shows that the gas-phase hydrogenation of an aldehyde is exothermic by 15 kcal., and of a ketone by 12 kcal. The free-energy change in the gas-phase hydrogenation of acetaldehyde to ethyl alcohol is -8.5 kcal., and of acetone to isopropyl alcohol -5.4 kcal. (Section 1.42). Thus, the equilibrium at 25° lies well on the alcohol side. The same is true of the liquid-phase hydrogenation, for which the values of ΔF are -10.0 and -6.0 kcal., respectively. When the temperature is raised, the equilibrium shifts toward the aldehyde (or ketone) side. However, if a rise in temperature is desirable in order to obtain a faster rate, increase in pressure will increase the amount of alcohol at equilibrium.

No reaction takes place at room temperature between hydrogen gas and an aldehyde or ketone. A catalyst is essential. The usual catalysts are copper chromite, or finely divided platinum or nickel. The rate of the reaction is increased by pressure or by heating. The rate also depends on various solvents in the following order: Ethyl alcohol > acetic acid > ethyl acetate > petroleum ether > ethyl ether > benzene.

19.15 Hydrogenolysis of Esters. In method f the hydrogenolysis is carried out at about 200–250°C. and at high hydrogen pressures (100 to 200 atm.) in the presence of a suitable catalyst such as copper chromite. An ester is more difficult to reduce than is an aldehyde or ketone. The gas-phase hydrogenolysis of an ester is exothermic to the extent of 12 kcal., as calculated from bond-energy and resonance-energy values. High-pressure hydrogenolysis is important industrially.

19.16 Reduction of Aldehydes and Ketones by Aluminum Isopropoxide. In method g the aldehyde or ketone is heated with aluminum isopropoxide dissolved in isopropyl alcohol. Reduction takes place, and the desired alcohol is formed as the aluminum salt. The aluminum then distributes itself between the two alcohols, that is, the product and the solvent. The original reducing agent is regenerated. Thus only a small quantity of the alkoxide is required, for it acts essentially as a catalyst.

If nothing is removed, the reaction comes to an equilibrium. The constant for the equilibrium in method g is given by the following expression:

$$K = \frac{[C_4H_9CH_2OH][(CH_3)_2CO]}{[C_4H_9CHO][(CH_3)_2CHOH]}$$

The value of the equilibrium constant can be calculated from known standard free-energy values of components (Section 1.4 and Table 1–3). If these are not known, an approximate value of ΔF may be obtained from bond energies and resonance energies. The value of $-\Delta H$ of hydrogenation of a gaseous aldehyde exceeds that of a gaseous ketone by 3 kcal. If the reasonable assumption is made that heats of vaporization cancel and that changes in entropy are alike, $-\Delta F$ for the over-all equation above in which an aldehyde is being reduced, would be 3 kcal., and K would be about 200 (see Equation 1–31). On the other hand, when a ketone is being reduced, presumably K would approximate unity. Since, therefore, a secondary alcohol is a better reducing agent than a primary alcohol in this type of reaction, the alkoxide of a secondary alcohol is generally used. The effect exerted by a change in temperature on the position of equilibrium is not extensive, since ΔH has such a small value, even when an aldehyde is being reduced.

The equilibrium reaction may be driven toward completion by either removing at least one of the products or increasing the concentration of one reactant, as has been discussed in Chapter 1. In any case the reducing alcohol is so chosen that the isolation of the desired product is rendered easy. Isopropyl alcohol is the most commonly used reducing alcohol, since (1) it is a secondary alcohol; (2) the corresponding ketone is the most volatile of the ketones and therefore most easily removed; (3) it is one of the lowest-boiling alcohols and can be easily removed from the product; (4) it is inexpensive. The low boiling point is sometimes a disadvantage since the reaction temperature and hence the rate is limited by the boiling point of the alcohol. Usually the reaction is continued until no more acetone can be removed. Then the desired alcohol is separated from the excess of isopropyl alcohol after the addition of water.

The aluminum alkoxides are prepared by dissolving clean aluminum in the anhydrous alcohol with the addition of a few crystals of mercuric chloride as a catalyst. The mixture boils from the heat of reaction. The alkoxides are low-melting solids and may be purified by distillation at reduced pressure.

19.165 Reduction of Aldehydes, Ketones, and Esters in Other Ways. Reduction of aldehydes, ketones, and esters also may be accomplished by metallic sodium and alcohol or sodium amalgam and water (or alcohol), method h. The solution must be buffered to prevent it from becoming too alkaline, since aldehydes and ketones may undergo condensation, and esters may be saponified. The yields are not so good as with aluminum isopropoxide.

The fermentation process by which sugar is converted into ethyl alcohol (Experiment 19–1) may be used for the reduction of aldehydes in general. These are added in small quantities directly to the vigorously fermenting liquid and are reduced to the corresponding alcohol along with acetaldehyde, which is an intermediate in the fermentation of sugar to ethyl alcohol. The over-all equations in the fermentation of sucrose are:

$$C_{12}H_{22}O_{11} + H_2O \rightarrow 2C_6H_{12}O_6$$

$$C_6H_{12}O_6 \rightarrow 2C_2H_5OH + 2CO_2$$
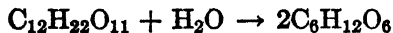
19.17 Addition of Hypochlorous Acid to Olefins. In method i acetic acid is added during vigorous agitation to an aqueous suspension of the olefin and calcium hypochlorite. Owing to the exothermic nature of the reaction, cooling is necessary. The reaction takes place rapidly. In the case of unsymmetrical olefins, addition takes place in two ways.

For example, with 2-pentene, 3-chloro-2-pentanol and 2-chloro-3-pentanol are formed. 3-Chloro-2-butanol is prepared by this method in Experiment 19–5. The β-chlorinated alcohols are important in the formation of epoxides (Chapter 22) which can react with Grignard reagents (method d) to form higher alcohols.

19.18   Side Reactions. In method a polymerization of the olefin may be troublesome since this reaction is promoted by the catalyst used in hydration. In methods b and c olefins often are formed, especially if the alkyl halide or ester is derived from a tertiary alcohol. Side reactions in the Grignard synthesis (method d) are discussed in Chapter 18. In methods e and f reduction to the hydrocarbons may take place. In method h aldehydes may undergo aldol condensation, and ketones the pinacol condensation. In method i some olefin dichloride is formed, owing to the presence of chloride ion in the hypochlorite. For this reason commercial products such as sodium hypochlorite solution or bleaching powder are less satisfactory than calcium hypochlorite which contains less chloride.

19.185   Recovery. Usually the alcohol is purified by distillation. Some precautions should be observed, since tertiary alcohols sometimes decompose. The tendency to decomposition is in the order: Tertiary > secondary > primary. Contamination of the alcohol by suspended matter or by an acidic substance usually lowers the temperature of decomposition. Even a primary alcohol if so contaminated may decompose if heated above 200°.

19.19.   Determination of Water in Alcohol. The water content in mixtures of water and alcohol can be ascertained by means of the specific gravity (Experiment 19–1). If the water content is quite small, 1% or less, it is more conveniently determined by titration with the Karl Fischer reagent. This is a solution of iodine and sulfur dioxide in a mixture of methanol and pyridine. The reaction is:

$$I_2 + SO_2 + 3C_5H_5N + H_2O + CH_3OH \rightarrow$$

$$3C_5H_5NH^+ + 2I^- + CH_3OSO_2O^-$$
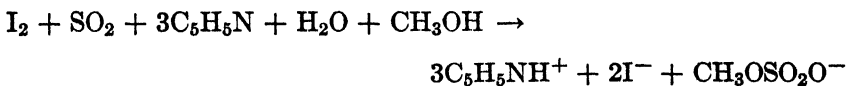
Ethyl alcohol forms with water an azeotropic mixture which boils at 78.15° and contains 95.57% alcohol by weight. The water content can be reduced to about 0.5% by refluxing with quicklime (Experiment 19–2).

Experiment 19–1   Alcohol by Fermentation

Dissolve 0.10 mole of cane sugar in about 300 ml. of water in a 500-ml. bottle or flat-bottomed flask. Add one fourth of a yeast cake ground

to a smooth paste with about 50 ml. of water, or, preferably, add 10 ml. of an active yeast culture; add 20 ml. of fermentation salt solution (Note 1).   Close the bottle with a tightly fitting stopper to which is fitted a bent glass tube leading to the bottom of a second bottle containing a solution of barium hydroxide, covered by a layer of kerosene. Let the solution stand until fermentation ceases, which may require 2 to 15 days (Note 2).   Observe and explain any change in the appearance of the liquids in the two vessels.

Remove most of the yeast by filtering into a large (preferably 1000-ml.) round-bottomed flask (Note 3), and collect the alcohol in a 100-ml. volumetric flask as a dilute aqueous solution, by distilling through a fractionating column.   Collect 100 ml. (Note 4).   While the distillation is in progress, become familiar with the different tables showing the specific gravities of water–alcohol mixtures (Note 5), and decide which one you will use.   *Thoroughly mix* the distillate, and test with litmus. If acidic, make basic, and redistil (Note 6), after adding some water.

Bring the liquid to the *temperature given in the table*.   Now determine the specific gravity of the liquid to the fourth decimal place, using either a Westphal balance or a pycnometer (Note 7).   From the table calculate the number of grams of alcohol obtained and the percentage yield.

To 20 ml. of the distillate add solid potassium carbonate as long as the salt dissolves.   If two layers form, separate, and test the lighter one for inflammability.   Prove the presence of alcohol in the original distillate, or in the lighter phase.

Notes

1. The solution of fermentation salts (Pasteur salts) is necessary for yeast growth. It contains 10 g. of ammonium tartrate, 2 g. of potassium phosphate, 0.2 g. of calcium phosphate, and 0.2 g. of magnesium sulfate per liter.

2. The optimum temperature of fermentation is 35°.   The more closely the fermenting liquid approximates 35°, the shorter the fermentation time.   During fermentation the liquid is cloudy; when fermentation ceases, the yeast settles to the bottom, and the liquid becomes clear.

3. This filtration will remove the greater part of the yeast cells.   It is not necessary that the filtrate be clear.   A heavy coarse filter paper, like E and D No. 617, especially if fluted, permits faster filtration than a finer-grained one.   Addition of a filter aid (see 5.25) is recommended.

4. Care should be taken not to lose any of the initial distillate.   Loss of some of the final distillate is not significant.

5. See tables in Landolt–Bornstein or in the chemical handbooks.

6. Adding base to the fermentation liquid may result in some ammonia distilling.

7. In determining alcohol in alcohol–water mixtures, generally use is made of specific-gravity measurements.   The Westphal balance is more rapid but is often inaccurate.   Check the balance against pure water before taking the reading on the alcohol.   By the use of the pycnometer the specific gravity determination is accurate to the fourth decimal place and fairly reliable to the fifth.   Yield, 85 to 90%.

Questions

1. Why not determine alcohol from the specific gravity of the fermentation liquid?
2. Explain why the distillate sometimes is acidic.
3. Why does the addition of potassium carbonate cause the formation of two liquid phases?
4. If the yield is not quantitative, how do you account for losses?
5. Explain the process of alcohol fermentation.
6. Is there a limit to the strength of an alcohol solution which can be produced by fermentation? Explain.

Experiment 19–2   Preparation of Absolute Ethyl Alcohol

Fit a 500-ml. round-bottomed flask with a reflux condenser, to the upper end of which is attached a calcium chloride tube. Put 300 ml. of 95 or 96% alcohol by volume (Note 1) in the flask, and add three times the theoretical amount of *good* quicklime in the form of small lumps (Notes 2 and 3). Heat the contents of the flask at the boiling temperature for 2 hours by means of a liquid bath (refer to 7.12), or, if the mixture is first allowed to stand overnight, it may be refluxed for 1 hour. Connect the flask to a *dry* condenser by means of a bent tube, the diameter of which should not be less than 8 mm., and provide the condenser with a receiver and calcium chloride tube, according to Figure 7–1 (Note 4). Distil over the alcohol (Note 5), discarding the first 10 to 15 ml. Determine the yield.

Determine the percentage of water by accurate determination of the specific gravity (see Experiment 19–1 and Note 7, Experiment 19–1) or by titrating with the Karl Fischer reagent (Note 6). To an accurately pipetted 10-ml. portion of the absolute alcohol (Note 7) add the reagent from a burette (Note 8) until the brown color persists (Note 9).

The alcohol, in a dry bottle with a tightly fitting cork stopper and with a label showing weight, percentage yield, and per cent of water, is turned in to the instructor.

Notes

1. Save about 10 ml. for tests later.
2. Test the lime by holding a small piece in a stream of tap water for 1 to 2 seconds and removing; a good quicklime should soon become hot.
3. In case only powdered quicklime is available, less may be taken (about twice the theoretical). Because of the greater surface, reaction is faster; therefore, more careful control is desirable.
4. The calcium chloride tube is not necessary if the humidity of the atmosphere is low (30%), as under these conditions little water is absorbed. The receiver may be closed with a plug of cotton.
5. The flask should not be heated with the direct flame, because of danger of breakage. An oil or wax bath at 110° will give a faster distillation than the water

bath. However, if the distillation is too rapid, the distillate is cloudy, owing to lime or perhaps a volatile calcium compound.

6. The Karl Fischer reagent is prepared by dissolving 85 g. of resublimed iodine in a mixture of 269 ml. of anhydrous pyridine and 667 ml. of anhydrous synthetic methanol, and passing in, while cooling in an ice bath, 64 g. of sulfur dioxide.

The reagent is standardized against a solution of water in methanol. First the methanol, in 10-ml. portions, is titrated against the reagent. Then 18.0 g. of water is added to methanol and made up to 1 liter with methanol. The solution is *thoroughly* mixed, and aliquots of 10 ml. are titrated. The resulting titer is the sum of that due to the water added, plus 98% of the original methanol titer. From this the titer due to the total water present can be calculated. This solution is kept in a tightly stoppered bottle and must be used for standardizing the reagent each day a titration is made.

7. The apparatus must be absolutely dry.

8. The reagent must be protected from moisture.

9. The color change is from the chrome yellow of the spent reagent to the brown of the iodine. Since 1 ml. of the reagent is equal to only a few milligrams of water, the end point does not need to be sensitive.

Questions

1. Why is the first part of the distillate rejected?

2. Can absolute alcohol be obtained by means of fractional distillation? Explain.

3. State whether or not the following substances could be used in place of quicklime under the conditions of this experiment, and give reasons for your answer: calcium chloride, calcium carbide, phosphorus pentoxide, concentrated sulfuric acid, anhydrous sodium sulfate.

4. Name some other substances besides calcium oxide which, after refluxing with 95% alcohol, allow absolute alcohol to be distilled off.

5. What volume of the Karl Fischer reagent corresponds to 0.1% of water in the alcohol, by this procedure?

Experiment 19–3 Preparation of Secondary Amyl Alcohol

Provide a 1-liter or 2-liter flask (Note 1) with a thermometer and a dropping (or separatory) funnel, and attach it by means of a short wide exit tube (10 to 15 mm. diameter) to a long condenser (90 cm.) arranged for distillation. Add sufficient water to give a final dilution to about 30% sulfuric acid. While performing the next part of the experiment, bring the water in the flask (Note 2) to boiling.

In a 1-liter or 2-liter flask cool to 20° or 25° sufficient 80% (by weight) sulfuric acid (Note 3) to furnish 2 to 3 moles of acid. To the acid add slowly, with *constant* and *vigorous* agitation, 0.50 mole of 2-pentene (Note 4) during the course of 15 to 20 minutes. In case the temperature rises above 25°, cool moderately, so that it is 20° to 25°. Continue the agitation until the pentene has reacted (Note 5).

The water should be boiling. Allow the reaction mixture to run into the hot water during the course of 5 to 10 minutes. The heat of dilution of the sulfuric acid should keep the solution boiling. If it does not, apply heat to keep the solution boiling, so that the alcohol is removed at once from the acid. After all the mixture has been added, continue the distillation as long as alcohol distils (Note 6), but at a slower rate, so as not to obtain a needlessly large volume of water.

Separate the two phases in a separatory funnel, running the water phase into a graduated cylinder. Note the volume. Add to the water phase a weight of sodium chloride sufficient to produce a half-saturated solution, close the graduate by placing the palm of the hand across the top, and by careful agitation cause the salt to dissolve. Determine the amount of the second phase which separates (data for question 10). Add this to the main portion of the alcohol.

Shake the combined portions with aqueous sodium (or potassium) carbonate until the alcohol layer tests neutral to moist neutral litmus paper (Note 7). Remove water in stages by shaking with *small* portions of a suitable drying agent (refer to 12.26 and 12.28), drawing off the aqueous phase each time.

Finally, even though the alcohol still contains a small amount of water, distil *slowly* from the proper-sized distilling flask with a very small flame. Some pentene distils at first, and later a cloudy distillate of the alcohol and water. Collect this separately until the temperature is constant near the boiling point of the alcohol, thus completely drying the main portion of the product (refer to 12.12). Dry the parts of the apparatus where moisture has condensed, and remove water from the cloudy distillate. Add this to the liquid in the distilling flask, and continue with the distillation as before. Collect over a 5° range near the boiling point of the alcohol. Calculate the percentage yield (Note 8).

Notes

1. A distilling flask, a Claisen flask, or a flask with two or three necks may be used. The path the vapor must travel between the surface of the liquid and the point of descent should be as short as possible, in order to minimize refluxing.

2. Do not add boiling chips or insoluble material. Refer to the preparation of olefins and to 14.165.

3. Add either c.p. or technical sulfuric acid slowly with *good* mixing under the tap to the proper amount of water, calculated on the basis of the acid composition, determined from a specific-gravity measurement. Be sure that the diluted acid is 80% by weight. Consult instructor if in doubt.

4. If the temperature is too low, the rate is slow, and, if too high, polymerization may take place. Mechanical agitation usually gives better results than does manual agitation. *Caution:* no flames near, due to fire hazard.

5. Usually 15 to 30 minutes is sufficient. The cloudiness which usually is associated with two liquid phases is barely observable here, owing to similarity of refractive indices. If uncertain, allow the mixture to stand undisturbed for a few minutes, to note if a second, lighter liquid rises.

6. This can be determined by collecting a small portion and noting the relative volumes of the two phases; also by noting when there is no change in the distilling temperature.

7. If any trace of acid is left in the alcohol, it will decompose during distillation.

8. Yield is 60%.

Questions

1. How is 2-pentene prepared?

2. Why not use concentrated instead of 80% sulfuric acid?

3. The reaction may be carried out by using a smaller weight of 80% acid. Do you see any advantage in using the larger amount?

4. Why not cool the mixture to 0°?

5. Why should the condenser be long?

6. Why is refluxing undesirable?

7. Why not add boiling chips to the hot water?

8. Why is it desirable to remove the alcohol rapidly from the hot dilute solution?

9. Explain why acid present in the alcohol during distillation will cause it to decompose.

10. Calculate from your data a minimum solubility of secondary amyl alcohol in water.

11. How does this compare with the actual solubility?

12. How do you account for any discrepancy?

13. In Experiment 14–3, 2-pentene was prepared from secondary amyl alcohol. Explain how it is possible to drive the reaction in either direction.

14. Is 3-pentanol the only component of secondary amyl alcohol?

15. What is formed when 3-pentanol is heated with dilute sulfuric acid and potassium dichromate?

16. How many reactions are involved in the formation of secondary amyl alcohol in this experiment? Write equations.

17. What is the function of sulfuric acid in this experiment?

18. Is the gas-phase hydration reaction (at 25°) endothermic or exothermic? Show how to calculate an approximate ΔH for the liquid-phase hydration.

19. What impurity or impurities are present in the crude and final products?

20. State the steps that have been taken to remove them.

Experiment 19–4   General Method of Preparing
Alcohols with the Grignard Reagent

2-Hexanol (Note 1)

Into the reaction flask holding the solution of the Grignard reagent from Experiment 18–1 (Note 2), pass all of the vapor of anhydrous acetaldehyde obtained by the decomposition of a 10 to 20% excess of

paraldehyde (see Note 3 and Experiment 25–4). The inlet tube for introducing the aldehyde vapor replaces the separatory funnel. It should be wide (12 to 14 mm. diameter), should extend well into the flask, and should end 1 or 2 cm. above the surface of the ether (Notes 4, 5, and 6). Stir the mixture *vigorously*, and cool it with an efficient cooling bath, which should be removed before the reaction is entirely finished so that the temperature of the mixture will rise. Finally heat with a bath of tepid water as long as any Grignard reagent remains. With the cooling bath and separatory funnel again in position, and with vigorous agitation, decompose the reaction product by running in from a dropping funnel the proper amount of water in the form of a 20 to 30% solution in methanol (Notes 7 and 8). In case the magnesium compound coagulates so that the ether separates well, pour the latter into another flask, for temporary storage.

Dissolve the insoluble magnesium compounds by adding dilute sulfuric acid with agitation and cooling (Note 9. *Caution:* See Experiment 6–1, Note 1). Drop the acid onto a moving part of the mass, near the stirrer. Separate the two layers in a large separatory funnel, add the main ether solution, and wash the combined ether phases by shaking several times with water until the magnesium sulfate is completely removed and then with aqueous potassium carbonate, until the ether phase is neutral to moist litmus paper. Dry the ether in stages by shaking with small amounts of anhydrous potassium carbonate or anhydrous magnesium sulfate, removing any aqueous phase that forms (Note 10). Let the ether stand overnight with additional drying agent in an Erlenmeyer flask large enough to give good contact with the drying agent. Remove the drying agent completely from the ether (Note 11).

Equip a two-necked flask with a dropping funnel and a fractionating tube having a packed column 25 to 30 cm. long, and provided with a cold-finger condenser at the top of the column. Attach a long (90-cm.) condenser. The flask should be large enough to hold conveniently the expected amount of alcohol (refer to 9.15). Strip off the ether while continually running in fresh solution, heating with a small flame. As soon as the boiling point rises above that of pure ether, collect the distillate in fractions. After the temperature has risen sufficiently, remove the column, and distil slowly through a short condenser, collecting the alcohol over a 5° range near the boiling point. Be on the alert for possible decomposition. In case the intermediate fractions are appreciable, refractionate by cuts in systematic fashion (refer to 9.13). Label the product properly, and calculate the percentage yield (Note 12).

Notes

1. Other alcohols may be prepared by this general procedure. Either or both of the reactants may be replaced, the butyl Grignard by some other Grignard reagent, the acetaldehyde by some other aldehyde or by a ketone, an ester or ethylene oxide, usually dissolved in two to three times the volume of absolute ether. Formaldehyde is used as the solid polymer, paraformaldehyde. In general the excess need not exceed 5 or 10%.

With ethylene oxide the reaction takes place in two steps. After the oxide has been added, the mixture must be heated to about 60°. Naturally ether must be removed by distillation (*Caution* as usual). Then a fairly vigorous reaction may set in. Therefore, one must be prepared to control the reaction at once by cooling moderately with a cold bath but not to stop the reaction. These directions are written for a solution of the Grignard reagent in ethyl ether.

2. The excess magnesium may remain when the added reagent is a saturated aldehyde or an ester. But it may reduce a ketone or an unsaturated aldehyde to the pinacol. In such cases the solution of the Grignard reagent is driven over by *dry* air into a second *dry* flask through dry glass tubing (see Experiment 18–2).

3. Or freshly distilled *anhydrous* liquid acetaldehyde may be diluted with 2 to 3 volumes of absolute ether and run in from a dropping funnel. Since acetaldehyde which has stood for some time often undergoes polymerization and then does not react properly, it is *unwise to use any but freshly distilled material.*

4. The addition compound is solid which easily clogs a narrow tube, especially if it dips under the surface.

5. The inlet tube is replaced by a dropping funnel if a liquid (aldehyde, ketone, or ester) replaces acetaldehyde gas. The liquid should be anhydrous and should drop directly onto an actively moving part of the reaction mixture, not onto the wall of the vessel, because a large solid mass would accumulate. The liquid should be diluted with 2 to 3 volumes of absolute ether, on account of the exothermic character of the reaction.

6. No inlet arrangement is necessary if paraformaldehyde is used. This should be anhydrous and may be added all at once, since it reacts but slowly. The mixture is agitated while heating until the solid disappears.

7. Do not use an unnecessarily large amount of methanol; otherwise, some of the desired product may remain in the aqueous phase when separation is made later.

8. The alcohol may be omitted and decomposition carried out with sulfuric acid directly (see discussion, Chapter 18). However, the evolution of hydrogen, resulting from the action of the acid on unreacted magnesium sometimes is quite violent in case too much acid is added.

9. Aqueous ammonium sulfate may be used instead (see Chapter 18). A disadvantage is the slow formation of magnesium carbonate in contact with carbon dioxide of the air. This, however, is not likely if the subsequent operations are carried out with reasonable dispatch.

10. Refer to Tables 12–2 and 12–3, and to Subsection 12.26.

11. Refer to 12.28. Tertiary alcohols and to a less extent secondary alcohols may decompose when attempt is made to distil them at atmospheric pressure, especially if a finely divided solid, or even a trace of acid, is present.

12. Yield is 70%.

Questions

1. Why should magnesium sulfate be removed completely?
2. Why should the ether solution not be acidic?
3. What is the reaction of ammonium sulfate and magnesium hydroxide?
4. Why may carbon dioxide react under these conditions and not if sulfuric acid is used instead of ammonium sulfate?
5. Would methanol alone react with the intermediate magnesium compound, and, if so, to what extent?
6. What advantage if any does the use of aqueous methanol have?
7. By what other methods may 2-hexanol be prepared?
8. What compound is formed when n-butyl magnesium bromide reacts with carbon dioxide? oxygen? allyl bromide? acetone?
9. What impurity or impurities are present in the crude and final product?
10. State the steps that have been taken to remove them.

Experiment 19–5   Preparation of 3-Chloro-2-butanol

Equip a 2-liter three-necked flask with dropping funnel, a Dry Ice condenser (Figure 7–2), and a sealed mechanical stirrer (Note 1), powerful enough to produce vigorous agitation in the viscous reaction mixture (Note 2). Be sure connections are air-tight. Rubber stoppers are permissible even though some butene is absorbed by the rubber (refer to Experiment 3–1, Note 4, or Experiment 15–1, Note 3, for drilling cork or rubber stoppers). Set the flask in a 2-gallon crock for a freezing mixture (preferably ice and hydrochloric acid), and set the whole high enough so that the crock sits on a stand and can be dropped by moving the stand to one side. It is well to set up the apparatus the day before, since the succeeding operations up to and including the drying of the solution of the product will take 2 to 3 hours. It is desirable to carry out these operations with reasonable dispatch and also to keep temperatures low to minimize loss from hydrolysis, especially under alkaline conditions.

Weigh an ampoule holding about 2 moles of butene, so that the weight may be checked later, after the ampoule has been emptied. Fit a stopper to the neck so that a tight fit results when it is inverted in a side neck of the flask later while being emptied.

While carrying out the next operations, cool about 2 liters of hydrochloric acid (Note 3) to about 5°, and cool the ampoule to the temperature at which it was sealed (Experiment 14–2).

Prepare a smooth, thin paste of H.T.H. (Note 4) and water in a 1-liter beaker by adding (Hood) 95% of the theoretical amount needed for the butene available to about twice the weight of water and ice, about half water and half ice. Stir vigorously to prevent local heating. Break up

all lumps. Dilute a 50% excess of acetic acid with enough water to make a 50 to 75% solution, and cool this (Note 5).

Fill the crock with crushed ice, and transfer the H.T.H. to the reaction flask. Load the Dry Ice condenser, first with Dry Ice, and then carefully add isopropyl ether. Draw off water from the crock, add more crushed ice, until full, pour in cold hydrochloric acid, and mix thoroughly. The cooling bath should be about −20°. Maintain good agitation within the flask and occasional good mixing of the outside bath from this point on. Just as soon as the inside temperature drops to 0° and before it goes below −5° (Note 6), add the butene by inverting the opened end of the ampoule into a neck of the flask (Note 7).

Allow acetic acid to flow in as rapidly as consistent with temperature control determined by rate of reflux. The time of adding the acetic acid should not be over 40 minutes. The bath temperature should not rise above −5°. When the reaction seems to slacken as indicated by a decrease in the rate of reflux, drop the bath. If kept too cool, calcium acetate may crystallize. Continue the addition until there is no further reaction.

Let stand quiet to see if the oil will separate. If it does not, slowly add about 20 ml. of glacial acetic acid with cooling and gentle stirring (Note 8). Transfer a small amount to a small separatory funnel to see if the emulsion breaks. If it does not, add more water and/or more acetic acid (refer to 6.16). In case a solid crystallizes, add water. It may be necessary to filter with suction to remove suspended matter, before the emulsion will break.

Finally separate the phases in a large separatory funnel, and extract the aqueous phase with four successive portions of isopropyl ether about 200 ml. each (Notes 9 and 10; refer to 6.15 and 6.17). Combine oil and extracts, remove calcium salts by shaking 3 or 4 times with about 150 ml. of water (sulfate-free), and then shake with aqueous potassium carbonate (about 1 M) until neutral. Dry in stages as rapidly and as completely as possible by shaking with small portions of potassium carbonate (Note 11; refer to 12.26).

Fractionally distil the product through an efficient column having 30 to 40 cm. of packing, and provided with cold finger condenser at the top. Set up the apparatus as in distillations at reduced pressure with air-tight (rubber) connections, and provide a bath (preferably an oil bath) for heating (read Section 8.2). Provide the flask with a satisfactory capillary air inlet for reduced pressure distillation (consult instructor). Remove as rapidly as possible at atmospheric pressure the azeotropic mixture of water and isopropyl ether at 59° to 62°, and isopropyl ether at 67°, without using the cold finger condenser. The bath

temperature slowly rises to about 90°. Then turn on the condenser, maintain a reflux ratio of 5 to 10, and slowly reduce the pressure so that distillation continues with the bath temperature about 90°.

With the pressure at 80 mm., collect a mixture of the isomeric 2,3-dichlorobutanes at 47° to 55° (Notes 12 and 13). At 30 mm. collect 3-chloro-2-butanol boiling at 50° to 58°. At 30 mm. collect 3-chloro-2-acetoxybutane (the acetate of the chlorohydrin) b.p., 60° to 70°. Increase the bath temperature if necessary to get a good rate of distillation. Wrapping the column is an aid, in case cooling is too extensive. Determine the weight of each fraction, properly label same, and hand in when reporting. Calculate the percentage yield of the chlorohydrin and the total percentage recovery from the butene (Note 14).

Notes

1. A mercury sealed stirrer or one equipped with an accurately fitted sleeve bearing may be used (refer to 15.17).

2. The stirring arms should have the widest possible sweep, preferably wide arms which fold, to permit entrance into the flask. Stirring is aided if the arms are hollow tubes, with an opening at the middle point.

3. Technical hydrochloric acid is satisfactory.

4. H.T.H. is a commercial product, 70% available chlorine. It contains sodium chloride as well as calcium hypochlorite. It is much more soluble in water than bleaching powder. The operations of weighing and mixing H.T.H. should be carried out in the hood, to prevent the dust escaping into the laboratory. The amount needed is calculated on the basis of available chlorine, that is, the weight of chlorine evolved when hydrochloric acid is added. Unless the sample is known to be fresh, *the hypochlorite content should be determined by analysis.*

5. Usually an excess of 5 to 10% is sufficient, but if the H.T.H. is below strength, more is necessary. Some water is desirable so that the acetic acid will not freeze when cooled.

6. Crystallization may start at a lower temperature.

7. *Caution:* Butene is highly inflammable, and butene–air mixtures can be highly explosive. Open the ampoule in the hood.

8. *Caution:* In case any H.T.H. remained unreacted at the end of the experiment, the chlorohydrin layer or the ether extract will have a greenish color. It must be kept cold until all chlorine and acid have been removed by washing; otherwise, a vigorous reaction may set in, with serious loss of product.

9. In case much water and/or acetic acid had been added, extract more than four times.

10. Isopropyl ether, on standing in the presence of air and light, forms peroxides which must be removed; otherwise, there is danger of an explosion towards the end of an ether distillation. Test a portion of the ether by shaking with acidified potassium iodide solution. If triiodide ion appears, remove peroxide by shaking with aqueous sodium bisulfite. Remove sulfurous acid completely with aqueous sodium hydroxide; otherwise, the finely divided precipitate which forms in the aqueous phase later greatly adds to emulsion difficulties. Ethyl ether may be used in place of isopropyl ether, but then water is not so easily removed.

11. The chlorohydrin hydrolyzes readily to 2,3-butanediol if it is wet and in the presence of alkali. If it is inconvenient to distil the preparation on the same day that it is made, store the well-dried solution in a cold room or refrigerator until it is distilled.

12. The shorter the packing, the higher should be the reflux ratio.

13. It might be better to distil at an even higher pressure, since there is some loss due to incomplete condensation when the distilling temperature is as low as 55°. 2,3-Dichlorobutane boils at 112–118° at 746 mm., and 3-chloro-2-butanol at 129–137°. Boiling points at other pressures can be obtained from Figure 8–2. Atmospheric pressure is undesirable since some of the product may decompose at the high temperature required.

14. The yield of chlorohydrin is 55%.

Questions

1. What is the reaction between acetic acid and calcium hypochlorite?

2. What is the reaction between acetic acid, calcium hypochlorite, and sodium chloride?

3. Why is acetic acid better than hydrochloric acid? than aqueous sulfuric acid?

4. What is the reaction between acetic acid, calcium hypochlorite, and 2-butene?

5. How can 2-butene be prepared?

6. Why should the temperature of the H.T.H. reaction mixture be 0° or lower before the butene is added?

7. What is bleaching powder?

8. Why is H.T.H. better than bleaching powder?

9. What insoluble precipitate may form if sulfurous acid remains in the isopropyl ether?

10. Explain how an ether peroxide can cause the formation of triiodide ion.

11. Why should calcium salts be removed?

12. Why not use calcium chloride to dry the ether solution?

13. What are the main impurities in the final product?

14. What steps have been taken to remove them?

Experiment 19–6   Properties of Ethyl Alcohol

A   SOLUBILITY IN LIQUIDS: *Commercial 96% Alcohol.*   Test the solubility of alcohol in water, sulfuric acid, methanol, benzene, carbon tetrachloride, kerosene, glycerol, etc. (Note 1).

Absolute Alcohol.   In a 10-ml. graduated cylinder test the solubility of absolute alcohol in kerosene, using 2.0 ml. of each. Record the volumes in your notebook. Add 1.0 ml. of water, shake, and let stand. Note the result. Record the volumes of the two phases in your notebook.

B   SOLUBILITY OF SOLIDS.   Try the solubility of some inorganic compounds, such as sodium sulfate, sodium chloride, fused calcium chloride, etc., in alcohol; also the solubility of some typical organic solids, such as acetanilide, benzoic acid, naphthalene, sucrose.

C TEST FOR WATER IN ALCOHOL: *96% Alcohol.* Add *ca.* 0.5 g. of anhydrous copper sulfate (Note 2) to 5 ml. of commercial 96% alcohol in a dry test tube, and close with a stopper. Agitate frequently. Note any color change during the course of 15 or 20 minutes (Note 3).

Place a small crystal of potassium permanganate in about 5 ml. of 96% alcohol, and agitate for a few minutes (Note 4).

Place a small piece of calcium carbide in a few milliliters of alcohol.

Absolute Alcohol. Repeat these tests with absolute alcohol. Note any differences.

D ALKYL HALIDE FORMATION. Mix 5 ml. of concentrated hydriodic acid (fuming, sp. gr. 1.7) with 5 ml. of alcohol in a test tube or small distilling flask. Warm with a very small flame, and after 1 or 2 minutes distil *slowly* through a glass tube, collecting the distillate in a small flask containing water. What is the distillate?

E OXIDATION OF ETHYL ALCOHOL. Heat in a test tube a mixture (well mixed) of 5 ml. of sodium dichromate solution, 5 ml. of 6 *N* sulfuric acid, and 1 ml. of alcohol. What are the evidences of chemical change?

F ETHYL ACETATE TEST. Add 1 ml. of concentrated sulfuric acid to a mixture of 1 ml. of alcohol and 1 ml. of *glacial* acetic acid in a test tube, and warm *gently* (do not boil). Let stand for a few minutes stoppered loosely, cool to 20° or lower, and then pour the contents into 5 ml. of cold half-saturated salt solution in another test tube. Note the characteristic odor of ethyl acetate (Note 5).

G IODOFORM TEST. To 0.5 ml. of 6 *N* sodium hydroxide (or equivalent) in a test tube add 2 drops of alcohol and then drop by drop a solution of iodine in potassium iodide until the solution is distinctly yellowish and remains so for 1 or 2 minutes. Heat gently to *ca.* 50°, and add more iodine solution if the solution becomes colorless. Set aside for some minutes. Note the color and odor of the precipitate (Note 6).

H SODIUM ETHOXIDE. To 1 ml. of absolute alcohol in a dry test tube add a piece of sodium about the size of a pea. Describe what happens. When the sodium has dissolved completely, add 5 ml. of water, and test with litmus. Explain. Repeat the experiment with 1 ml. of absolute alcohol, adding sodium until no more dissolves while warm. Close the tube with a stopper and allow to cool.

Notes

1. Perform solubility tests (see Experiment 2–1) so as to detect moderate solubility, as well as low solubility or complete miscibility. Note that a turbidity or emulsion may be due to the presence of a small amount of water which was dissolved in one liquid but insoluble in the second.

2. Prepare anhydrous copper sulfate by heating the pentahydrate in a porcelain dish over a flame.

3. The test is more delicate if the ratio of alcohol to anhydrous copper sulfate is larger.

4. The slow precipitation of manganese dioxide is due to the reduction of permanganate by the alcohol; it need not be considered as part of the test.

5. The changing of a substance into a compound possessing a characteristic odor is a valuable aid in its identification but is not an absolutely reliable test. Whenever possible the compound to be identified should be converted into a solid substance, which possesses a definite melting point.

6. Most compounds containing the CH_3CO- and CH_3CHOH- groups joined to carbon or hydrogen yield iodoform; acetone and isopropyl alcohol react more rapidly than does ethyl alcohol.

Questions

1. What types of organic compounds have low solubilities in 96% ethyl alcohol?

2. How do you account for the different solubilities in kerosene of 96% and of absolute alcohol?

3. Judging from your results, which is the better solvent for alcohol: water or kerosene? Explain.

4. Is there any connection between the solubility of an inorganic salt in water and its solubility in alcohol? Discuss.

5. What is the explanation for the changes observed in C?

6. Does ethyl alcohol resemble an acid in any of its reactions; a base?

7. In which of the above experiments is an ester formed?

8. What are the oxidation products of ethyl alcohol?

9. Write balanced equations for the reactions in D, E, F, G, and H. Use the actual reagents.

Chapter 20

ACIDS

Acids may be prepared by: (a) hydrolysis, or saponification of their esters; (b) the nitrile synthesis and hydrolysis of the resulting nitriles, (c) carbonation of Grignard reagents. (d) oxidation of aldehydes or primary alcohols, (e) oxidation of olefins, (f) the malonic ester or acetoacetic ester synthesis (Chapter 40).

(a)
$$CH_3COOC_2H_5 + H_2O \rightarrow CH_3COOH + C_2H_5OH$$

$$(C_{15}H_{31}COO)_3C_3H_5 + 3NaOH \rightarrow$$
$$3C_{15}H_{31}COONa + C_3H_5(OH)_3$$

$$C_{15}H_{31}COONa + H_2SO_4 \rightarrow C_{15}H_{31}COOH + NaHSO_4$$

(b)
$$C_2H_5I + KCN \rightarrow C_2H_5CN + KI$$

$$C_2H_5CN + KOH + H_2O \rightarrow C_2H_5COOK + NH_3$$

$$C_2H_5COOK + H_2SO_4 \rightarrow C_2H_5COOH + KHSO_4$$

(c)
$$C_2H_5I + Mg \rightarrow C_2H_5MgI$$

$$C_2H_5MgI + CO_2 \rightarrow C_2H_5COOMgI$$

$$C_2H_5COOMgI + H_2SO_4 \rightarrow C_2H_5COOH + IMgSO_4H$$

(d)
$$3C_2H_5CH_2OH + 4KMnO_4 \rightarrow$$
$$3C_2H_5COOK + 4MnO_2 + KOH + 4H_2O$$

$$3C_2H_5CHO + 2KMnO_4 + KOH \rightarrow$$
$$3C_2H_5COOK + 2MnO_2 + 2H_2O$$

$$C_2H_5COOK + H_2SO_4 \rightarrow C_2H_5COOH + KHSO_4$$

(e) $\quad 3C_2H_5CH{=}CHC_2H_5 + 8KMnO_4 \rightarrow$
$$6C_2H_5COOK + 8MnO_2 + 2KOH + 2H_2O$$

20.11 Hydrolysis and Saponification of Esters. Method a is discussed in Chapter 19 and 21. This is an important way of preparing

acids, since many fatty acids occur naturally in the form of fats, which are glyceryl esters of the acids. When these are saponified, usually mixtures of salts of the fatty acids are obtained, which yield the mixed fatty acids on the addition of a mineral acid. The recovery of a pure acid from these mixtures usually is tedious.

20.12 Nitrile Synthesis and Hydrolysis of Nitriles. These steps of method *b* are discussed in Chapters 28 and 27 (see also 37), respectively.

20.13 Carbonation of Grignard Reagents. In method *c* carbonation may be carried out by either (1) passing carbon dioxide into the cold ether solution of the Grignard reagent (Chapter 18), or (2) pouring the ether solution with vigorous agitation onto freshly pulverized solid carbon dioxide, taking care to prevent access of moisture. Since the reaction is strongly exothermic, and since the principal side reaction, that of ketone formation which results from the action of a second molecule of the Grignard reagent,

$$C_2H_5C\!\!-\!\!OMgBr + C_2H_5MgBr \rightarrow$$
$$\overset{\|}{O}$$

$$(C_2H_5)_2C\!\!-\!\!OMgBr \xrightarrow{\ H_2O\ } (C_2H_5)_2C\!\!=\!\!O$$
$$\underset{OMgBr}{|}$$
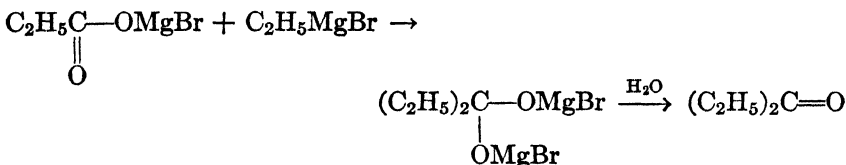
takes place at room temperature, control of the temperature is desirable. Thus the ethyl Grignard yields diethyl ketone as well as propionic acid at room temperature. In this case the ketone is the main product when the carbon dioxide is passed slowly into the heated solution. To obtain good yields of acids, therefore, a low temperature ($-80°$) is desirable. The superiority of procedure 2 rests not only on temperature, but also on concentration control. Of course, it is necessary to decompose the addition compounds with water and mineral acid in order to isolate the ketone and the organic acid.

20.14 Oxidation of Aldehydes or of Primary Alcohols. In method *d* oxidation can be accomplished with dichromate or permanganate. Dichromic acid (chromic acid mixture, from an alkali dichromate, sulfuric acid and water) attacks primary alcohols with the formation of aldehydes. The rate of reaction increases rapidly with hydrogen-ion concentration. Aldehydes also are oxidized by the mixture, but apparently at a slower rate. For good yields of acids, the aldehyde must not be allowed to escape.

Potassium permanganate under alkaline conditions converts primary alcohols directly to acids. If all the potassium permanganate is dissolved initially, the volume is so large that recovery of the acid is tedious.

However, even under these conditions the reaction is complete in 8 or 10 hours at 5°. Under these conditions yields are good (85%). If a smaller volume of water is used, so that most of the permanganate initially is undissolved, the reaction takes place rapidly. However, under these conditions, the yields are lower, owing to oxidation of some of the acid. Nevertheless, this procedure is justified with inexpensive alcohols, as *n*-propyl alcohol (Experiment 20–2), not only because of the faster rate, but also because of the saving of time in evaporation of the water. The recovery of propionic acid in an anhydrous form is not so easy as the differences in boiling points of water and the acid would suggest, because of the association tendencies of both. In the experiment described, the water is largely eliminated as a constant-boiling mixture with isopropyl ether (refer to 12.12, Drying by Distillation).

20.15   Oxidation of Olefins. In method *e* oxidation can be carried out in much the same way as with an alcohol or aldehyde. This method is useful for preparing acids from naturally occurring unsaturated compounds. When unsymmetrical olefins are oxidized, mixtures of acids are obtained. These are more difficult to separate than differences in their boiling points indicate, owing to the association of the acid molecules.

20.16   Thermochemistry. The heat effects in methods *a*, *b*, and *c* are discussed in the chapters to which reference has been made. An approach to the energy changes in oxidation reactions can be made on the basis of bond energies and resonance energies by considering gaseous oxidations with molecular oxygen.

<div align="center">

TABLE 20–1

HEAT EFFECTS IN GAS-PHASE OXIDATIONS WITH O_2

</div>

Reaction	ΔH, kcal. Over-all	Per COOH
$RCH_2OH + O_2 \rightarrow RCOOH + H_2O$	−108	−108
$2RCHO + O_2 \rightarrow 2RCOOH$	−128	−64
$RCH{=}CHR + 2O_2 \rightarrow 2RCOOH$	−210	−105

From Table 20–1 it is evident that all three reactions are strongly exothermic.

When oxidizing agents are employed, as for example potassium permanganate in basic solution, or dichromate in acid solution, ΔH, as calculated from heats of formation, is even more negative. With alkaline permanganate, ΔH per mole of salt formed from a primary alcohol or from an olefin is approximately −150 kcal., and with acid dichromate ΔH per mole of acid formed is approximately −140 kcal. These values

are so large that control of rate is important. However, in case a relatively large amount of water is present, as for example in the oxidation of an alcohol with potassium permanganate completely dissolved in water, the high dilution by the water so lowers the rate, and the large volume of water constitutes such a big heat reservoir, that little temperature change is noted. But, when the oxidation is carried out in fairly concentrated solution, as in the oxidation of 1-propanol with alkaline permanganate (Experiment 20–2), care must be taken that the reaction does not get out of hand. In the last instance a metal container is desirable, in order to obtain satisfactory heat transfer.

20.17 Formic Acid from Oxalic Acid. When oxalic acid is heated, it undergoes decarboxylation to formic acid, but the operation is not satisfactory since oxalic acid sublimes, and some of the formic acid may decompose also. The decarboxylation proceeds smoothly in glycerol solution (Experiment 20–1), through a series of reactions. The ester, glyceryl monooxolate, is formed first. This decarboxylates smoothly and at a relatively low temperature to glyceryl monoformate. On the addition of more oxalic acid, formic acid is obtained on heating. Oxalic acid may replace formic acid from the ester, thus regenerating glyceryl oxalate, or water, if the oxalic acid is hydrated, may cause hydrolysis of the formate ester to formic acid and glycerol, which then can react with oxalic acid, regenerating glyceryl oxalate. Other esters may be present also, as dioxalates, diformates, and so on.

$$CH_2—CH—CH_2 + COOH \longrightarrow CH_2—CH—CH_2 + H_2O$$
$$\quad|\qquad|\qquad|\qquad\quad|$$
$$OH\quad OH\quad OH\quad COOH \qquad OH\quad OH\quad O—CO—COOH$$
$$\text{glyceryl monooxalate}$$

$$CH_2—CH—CH_2 \longrightarrow CH_2—CH—CH_2 + CO_2$$
$$\quad|\qquad|\qquad|\qquad\qquad\quad|\qquad|\qquad|$$
$$OH\quad OH\quad O—CO—COOH \qquad OH\quad OH\quad O—CHO$$
$$\text{glyceryl monoformate}$$

$$\xrightarrow{H_2O} CH_2—CH—CH_2 + HCOOH$$
$$\qquad\qquad\quad|\qquad|\qquad|$$
$$\qquad\qquad\quad OH\quad OH\quad OH$$

$$CH_2—CH—CH_2$$
$$\quad|\qquad|\qquad|$$
$$OH\quad OH\quad O—CHO \quad \xrightarrow{(COOH)_2} CH_2—CH—CH_2 + HCOOH$$
$$\qquad\qquad\qquad\qquad\qquad\qquad\quad|\qquad|\qquad|$$
$$\qquad\qquad\qquad\qquad\qquad\qquad OH\quad OH\quad O—CO—COOH$$
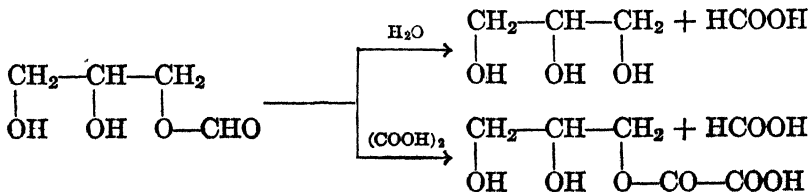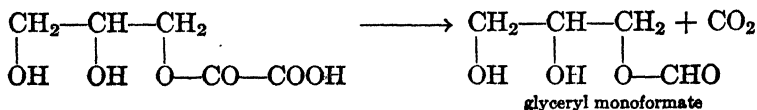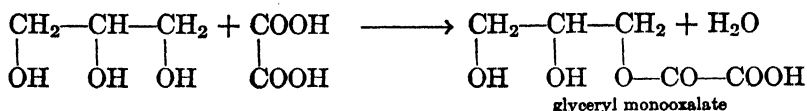
20.18 Neutralization Equivalent of an Acid. This is the weight in grams that neutralizes one equivalent weight of a strong base. The neutralization equivalent often is of value in identifying an unknown acid or in establishing the purity of a known acid.

Experiment 20–1   Preparation of Formic Acid

Dehydrate 50 g. of glycerol by heating in an open dish until a thermometer placed in the glycerol registers 175° (Note 1). After the glycerol has cooled, pour it into a 250-ml. distilling flask which contains 0.5 mole of oxalic acid dihydrate (Note 2). Connect the flask as in distillation except that the bulb of the thermometer should be below the surface of the liquid. Heat with a low flame until the temperature rises slowly to 115°, and collect any distillate in a flask. Cool to about 80°, add another 0.5 mole of oxalic acid, and distil again, until a temperature of 115° is shown by the thermometer. Collect the distillate with the previous one. Repeat once more, this time carrying the temperature to the point where the distillation of the acid practically ceases (140° to 150°; Note 3). Measure the volume of the combined distillates after mixing thoroughly, for the last portions are more concentrated. The residue in the distilling flask is placed in the bottle marked "Formic Acid Residues" to be saved for the preparation of more formic acid.

Divide the solution of formic acid into two portions, the smaller constituting about one fifth of the total. Use the smaller fraction for analysis, and save the larger portion for Experiment 20–3.

Determine the concentration of formic acid either by titration with a base, using phenolphthalein as an indicator, or preferably by another method which is based on some one of the numerous other reactions of formic acid (Note 4). From the result calculate the per cent of formic acid in the distillate and the percentage yield of formic acid (Note 5).

Notes

1. Or 50 g. of the "Formic Acid Residues" left over from previous experiments may be used. It is not necessary to dehydrate this, as it is used directly. In this case, the preliminary heating to 175° is omitted; instead the first portion of oxalic acid is added, the temperature is taken at once to 140° to 150°, and any distillate is collected. The mixture is cooled to about 115° before the next portion is added.

2. Anhydrous oxalic acid also may be used.

3. The temperature must not be too high; otherwise, decomposition to allyl alcohol takes place.

4. Since this will require more time and may involve setting up apparatus, it should be attempted only by the better-qualified students. Consult the instructor.

5. The yield is 30 to 35% when glycerol is used and much higher (80 to 90%) if one starts with the "Formic Acid Residue." The yield is calculated on the basis of oxalic acid taken. No correction is made for the amount of acid in combination with the glycerol. This is a variable amount, owing to the existence of a variety of esters of glycerol.

Questions

1. Explain why the addition of glycerol is desirable.
2. What is the compound first formed?
3. How is formic acid obtained from it?
4. What other compound or compounds may be formed from oxalic acid and glycerol?
5. Explain why the yield is low when glycerol is used.
6. Explain why the yield is higher when "Formic Acid Residues" are used.
7. What grouping of atoms is characteristic of organic acids?
8. How does formic acid differ structurally from other organic acids?
9. What is the effect of temperature on (a) formic acid, (b) sodium formate?
10. What are the general reactions by which fatty acids may be obtained?

Experiment 20-2   Preparation of Propionic Acid

OXIDATION OF n-PROPYL ALCOHOL.   On a small ring stand which, with the necessary rings, will sit inside a 4-gallon crock, fasten securely, by means of two rings, one above and one below, a metal can about 6 inches in diameter and 7 inches tall (Note 1), with a clearance of about 1 inch at the bottom.   Set the ring stand and can within the crock, and provide a mechanical stirrer of sufficient power to produce vigorous agitation in the final thick paste of hydrated manganese dioxide and water (Note 2).   Finely pulverize an amount of potassium permanganate which is a 10% excess over the amount theoretically required.   Surround the can with a good freezing mixture of ice and salt to a height of 1 to 2 inches.   In the can place 0.5 mole of potassium hydroxide (Note 3), about 0.5 kg. of finely chopped ice, and 1.0 mole of n-propyl alcohol (Note 4).

Start adding the permanganate immediately after the other ingredients have been added and before the mixture becomes too cold.   If the temperature gets too low, that is, much below 0°, oxidation may be so slow that the permanganate does not react and thus accumulates, to give an uncontrolled reaction later.

Without delay, and while stirring as rapidly as possible, add the finely pulverized potassium permanganate (Note 5) in approximately 10-g. portions until the temperature rises to 25°.   Keep the temperature at about 25° by continually adding permanganate and ice until all of the former and about 1 kg. more of the latter are used (making 1.5 kg. of ice altogether).   At frequent intervals loosen any deposit at the bottom of the can by means of a heavy stirring rod.   The addition will take about 1 to 1.5 hours.   Allow the stirring to continue for another half-hour, keeping the temperature at 20° to 25°.   If necessary, add more ice to the cooling bath, which should be stirred frequently.

Filter out the manganese dioxide with suction, using a large (8-inch) Buechner funnel fitted onto a 2- or 3-liter suction flask (Note 6), and continue until no liquid flows (refer to Section 5.4). Wash the precipitate thoroughly with three portions of water, at least 100 ml. each, preferably removing the filter cake each time to a suitable vessel, in which the solid and liquid can be well mixed. Remove as much water as possible each time by suction. Make the combined filtrates slightly acidic with dilute sulfuric acid. Warm slightly to remove carbon dioxide, and make *slightly* basic to phenolphthalein with potassium hydroxide solution. The liquid may stand at this point.

Evaporate fairly rapidly in a large (20-inch) evaporating dish (*Caution:* Note 7), until the volume is 100 to 150 ml. (Note 8). Let potassium sulfate crystallize, and remove it by suction filtration. Continue with the evaporation in a smaller vessel, if desired, until all water is removed. Avoid local overheating after solid has separated, or as the concentration of potassium propionate becomes high; otherwise, decomposition may take place. Determine the weight of dry potassium propionate, taking into account the weight of potassium sulfate present.

ISOLATION OF ANHYDROUS PROPIONIC ACID. (See also Note 9.) To the dry potassium propionate in a beaker add slowly, with thorough mixing and cooling, the correct amount of sulfuric acid, which, if concentrated, should be somewhat less (10 to 20%) than that required to convert potassium propionate to potassium bisulfate and, if about 75% acid, should be somewhat more (20 to 40%) than that required to form potassium sulfate (Note 10). Be sure that reaction is complete. With the concentrated acid it is necessary to transfer the mass to a mortar and grind until all lumps are gone and until the mass appears homogeneous. This is desirable also with 75% acid, for then reaction is more complete.

Extract the propionic acid from the salt cake by stirring it with 100 to 150 ml. of a suitable solvent, such as ethyl ether, isopropyl ether, or benzene (*Caution:* no flames near; Notes 11 and 12), and then removing the solid by gentle suction filtration with minimum evaporation of solvent (Note 13). Repeat with successively smaller volumes of solvent until the propionic acid is largely removed. It is important to press out as much liquid as possible each time.

Fractionally distil through an efficient column (refer to 9.15 and Section 9.2), preferably a 1-foot Vigreux column with Claisen top and reflux condenser (Note 14). Use a high reflux ratio. In case isopropyl ether or benzene is the solvent, distil the respective azeotropic mixture until all water is removed, adding more of the solvent, if necessary (Note 15). Then remove excess solvent. After that the temperature

should rise rapidly to near the boiling point of propionic acid (Note 16). Collect over a 3° range near the boiling point (Note 17). If the temperature rise is slow near 130°, make a cut, so as to recover product by redistillation in case there is a sizable fore run.

If ethyl ether is the extracting solvent, add either isopropyl ether or benzene before distilling. After ethyl ether is removed, proceed as in the foregoing.

From the weight of propionic acid calculate the percentage yield. Label the product in the usual way.

Notes

1. An empty 3-quart fruit can serves admirably.

2. The stirrer should be set off center in order to minimize vortex action and as close to the bottom as possible.

3. Technical potassium hydroxide is satisfactory.

4. *n*-Propyl alcohol often contains water. The density should be taken at the proper temperature and the purity of the alcohol determined from the known relationship of density to composition (See *International Critical Tables*, Vol. III, page 112).

5. An excess of permanganate is necessary, possibly because it slowly attacks potassium propionate. The mixture, after reaction is over, should not stand overnight.

6. This *must be trapped* to prevent water from being sucked back through the aspirator; this often happens when the water is turned off or when the pressure drops.

7. These large dishes sometimes break unexpectedly. This seems to be more likely when the support is an iron ring, especially a small one.

8. If the first part of the evaporation were carried out as a distillation, unreacted propyl alcohol would be recovered in the form of a dilute aqueous solution. The amount recovered could be calculated from the density of the distillate. The amount of permanganate dissolved in the filtrate is insignificant.

9. Also, propionic acid may be obtained from potassium propionate by one of the two following procedures: (a) Mix the latter with an excess (20 to 30%) of anhydrous potassium bisulfate; both solids should be finely ground first and then intimately mixed; place the mixture in a short-necked flask, and distil over the propionic acid by heating, with a bare luminous flame; (b) mix with about 0.6 or 0.7 mole of cold concentrated sulfuric acid in a short-necked flask from which the distillation is to be made; the salt should be finely ground first and then *thoroughly* mixed with the acid; distil the wet propionic acid as previously. The recovery usually is lower than by extraction.

10. When water is present, as in 75% acid, reaction between potassium propionate and potassium bisulfate can take place slowly; consequently, potassium sulfate is formed. But in the absence of water it is necessary to heat these two salts dry (see Note 9), in order to obtain reaction. Thus about 1 mole of concentrated sulfuric acid is necessary, if the mixture is not heated. But, since reaction may be incomplete, a deficiency is desirable, for propionic acid is difficult to recover if any unreacted sulfuric acid is present, owing to the high mutual solubilities of the two acids.

An advantage of concentrated sulfuric acid is easier extraction of propionic acid

from the salt cake, since propionic acid is miscible with water. An advantage of 75% acid is more complete reaction, and thus more propionic acid formed.

11. Ethyl ether is a better solvent than either isopropyl ether or benzene for propionic acid. However, its high volatility is a disadvantage; also the greater solubility of water in it, in comparison to the other two solvents. Isopropyl ether is a better solvent than benzene for propionic acid but dissolves more water.

12. Isopropyl ether usually contains some peroxide which may cause a dangerous explosion when evaporated to a small residue. The ether should first be shaken with a satisfactory reducing agent, for example aqueous sodium bisulfite or acidified ferrous sulfate (Experiment 19–5, Note 10, p. 223).

13. A powerful suction is to be avoided, because of the volatility of the solvent. Preferably a rubber dam should be used (refer to Section 5.4).

14. A column of glass rings is less desirable, because of the much larger holdup. On this account, much propionic acid is lost at the end. To avoid loss due to a large flask it is desirable to use a flask somewhat larger than needed to hold the expected amount of product and run in continuously some of the solution while the solvent is being stripped off.

15. The azeotropic mixture of isopropyl ether and water distils at 62° and contains 4.5% water. The one of benzene and water distils at 69° and contains 8.9% water. Both separate into two phases on cooling. Azeotropes of propionic acid with isopropyl ether and benzene are not described. If they exist, the one with benzene probably would contain less than 0.5% propionic acid, and certainly more than the one with isopropyl ether.

16. This is in sharp contrast to the difficulty of separating propionic acid and water by distillation.

17. Weight of product, b. p. 138–141°, is about 50%.

Questions

1. Why is a metal can used in preference to a glass beaker?

2. Why is an excess of permanganate desirable?

3. In many operations, excess of permanganate is often reduced by adding ethyl alcohol. Why not do so in this experiment?

4. What is the solubility of potassium permanganate in water at 25°?

5. What is the approximate solubility of potassium permanganate in the reaction mixture?

6. What weight of potassium permanganate is in solution in the final reaction mixture, assuming quantitative oxidation of the alcohol?

7. Why is it not desirable to add merely enough sulfuric acid to the solid potassium propionate to just produce an acid reaction?

8. What solid separated during or after the addition of sulfuric acid?

9. Would there be any advantage in using phosphoric acid in place of sulfuric acid?

10. Any disadvantage?

11. Would there be any advantage in using ethyl alcohol in place of isopropyl ether?

12. Any disadvantage?

13. What advantage does 75% sulfuric acid have over concentrated acid?

14. What disadvantage?

15. What products are formed when *n*-propyl alcohol is oxidized by an aqueous solution of sodium dichromate and sulfuric acid?

16. By what other process may propionic acid be prepared?

17. Write the formula and the name of the radical which is characteristic of organic acids.

18. What are the probable impurities in the crude and final products?

19. What steps have been taken to remove them?

Experiment 20–3   Properties of Formic Acid

The dilute solution obtained from Experiment 20–1 when submitted to fractional distillation gives a solution of constant boiling point 107° and containing 77% formic acid. For the following experiments use the dilute solution, or constant-boiling formic acid diluted with water:

A   REDUCTION OF SILVER ION.   To a mixture of formic acid and silver nitrate solutions add 6 *N* ammonium hydroxide, drop by drop, until any silver hydroxide that precipitates has dissolved in the excess of base.   Heat the solution, and set aside.

B   REDUCTION OF MERCURIC ION.   Shake for about 1 minute 2 ml. of the distillate with 0.1 or 0.2 g. of mercuric oxide.   Filter the solution, and heat to boiling.

C   DECOMPOSITION OF FORMIC ACID BY SULFURIC ACID.   To 1 ml. of the distillate in a test tube, which preferably is closed by a stopper carrying a short glass tube, add 5 to 10 ml. of concentrated sulfuric acid with cooling; heat gently.   Apply a flame to the gas evolved.   If the results are negative, repeat the experiment, using 0.5 g. of sodium formate instead of the 1 ml. of formic acid solution.

D   POTASSIUM PERMANGANATE AND A FORMATE.   Neutralize 1 ml. of the distillate with a dilute solution of sodium hydroxide, and add drop by drop a solution of potassium permanganate (Note 1).

E   SALTS OF FORMIC ACID.   Divide the remainder of the distillate into two parts (measure), and from the data obtained in Experiment 20–1 calculate the weights of cupric oxide and lead monoxide that will neutralize the formic acid in the respective solutions.   Then take a *small* excess of oxide, and add the formic acid solution, which in the case of the lead oxide should be diluted with much water (Note 2).   Heat each mixture until the formic acid is converted into a salt, adding a little more oxide if necessary and avoiding decomposition, which will be evident if an amorphous precipitate forms or if the liquid appears to be boiling much below 100°, since the gas evolved will then be due to decomposition (Note 3).   Filter the solutions while hot, and permit the products to crystallize (refer to 5.24 and Section 5.4).   Obtain additional materials by working up the mother liquors (Note 4).   From the weight

of each salt calculate a yield of formic acid obtained in Experiment 20–1, and compare w'th the yield as calculated in Experiment 20–1. How do you account for any difference?

Notes

1. The permanganate (Baeyer) test for unsaturation is meaningless except for hydrocarbons.
2. The solubility of the lead salt in water is 1.6 g. at 16°, 2.8 g. at 25°, and 18 g. at 100°.
3. If decomposition takes place, lower the temperature, and stir frequently.
4. Evaporation at room temperature avoids decomposition. If this is done, the dish should be covered to keep out dust.

Questions

1. Write equations for the reactions in A, B, C, D, and E.
2. What properties of formic acid do each of these experiments show?
3. Which of these properties do fatty acids in general possess?
4. Why is more water used with lead oxide than with copper oxide?
5. Why is frequent stirring desirable while dissolving the oxides?
6. What is the objection to allowing the crystallization to proceed by evaporation at room temperature?
7. How may anhydrous formic acid be obtained from any of the substances prepared in this experiment?
8. Can formic acid be prepared by oxidizing methyl alcohol with an excess of potassium permanganate?
9. Describe explicitly how you would recover the formic acid in a more or less anhydrous form from 1 mole of sodium formate.

Experiment 20–4   Properties of Glacial Acetic Acid

A SOLUBILITY. Test the solubility of glacial acetic acid in water, alcohol, ether, and gasoline. Test its solubility also in chloroform, using equal volumes (about 2 ml. of each) in a small graduated cylinder. To this resulting solution add a definite volume (0.5 to 1.0 ml.) of water, a few drops at a time. Mix well each time, and note the results.

B FREEZING POINT. To an ordinary-size dry test tube fit a cork stopper carrying a thermometer. Place in the tube 5 to 10 ml. of an acetic acid unknown (enough to cover the bulb of the thermometer; Note 1). Surround the tube with chipped ice and water. As the temperature drops below 15°, stir with the thermometer, rubbing the inner wall of the tube to induce crystallization. As soon as crystals form, remove the tube from the freezing mixture. Agitate while the

acid melts, and note the temperature when almost all of the acid is melted (Note 2).

Making use of Equation 4–2, calculate the per cent of water in the acetic acid.

Allow the test tube containing the acetic acid to stand open to the air for ½ to 1 hour with occasional agitation; repeat the determination of the freezing point.

C   ACETIC ACID AND OXIDIZING AGENTS.   Test the action of glacial acetic acid towards these oxidizing agents: neutral aqueous potassium permanganate, acidic aqueous potassium permanganate, and acidic aqueous sodium dichromate, adding more sulfuric acid and heating if there is no reaction cold.   Repeat with formic acid.

D   ACETIC ACID AND BROMINE.   To 1 ml. of acetic acid in a test tube add 1 or 2 drops of a solution of bromine in carbon tetrachloride; note any results.

Notes

1. Obtain from the instructor a sample of a mixture of acetic acid and water.

2. The amount of solid should not be too small; otherwise, an error may be introduced that results in a high reading.   However, a satisfactory reading with only a small amount of solid present may be obtained if the tube is immersed in water at a temperature only slightly below the temperature of the acetic acid–water mixture. (Refer to Section 4.1.)

Questions

1. What is the significance of the word "glacial" when applied to acetic acid?

2. Why do the first few drops of water dissolve in the mixture of acetic acid and chloroform?

3. Why do two phases result after about 0.5 ml. of water has been added?

4. What statement can be made in regard to the relative solubilities of acetic acid in water and in chloroform?

5. In determining the freezing point, why should the reading be taken when the solid has largely disappeared?

6. Why may the reading be high if taken when most of the solid has melted?

7. Was there any change in the melting point of the acetic acid on standing? Explain.

8. Can the per cent water in all mixtures of acetic acid and water be determined by specific-gravity measurement, in a manner similar to the determination of alcohol in aqueous alcoholic solutions?

9. Compare ethyl alcohol, formic acid, and acetic acid in their behavior towards oxidizing agents.

10. What class of organic compounds already studied does acetic acid most resemble in its behavior towards oxidizing agents and bromine?

11. What are the sources of acetic acid?

Chapter 21

ESTERS

Esters may be prepared by: (*a*) the reaction of alkyl halides with the salts of organic acids, (*b*) the addition of acids to olefins, (*c*) the alcoholysis of acid chlorides or acid anhydrides, (*d*) the alcoholysis of nitriles, (*e*) esterification of alcohols by acids.

(*a*) $$CH_3COONa + IC_2H_5 \rightarrow CH_3COOC_2H_5 + NaI$$

(*b*) $$CH_3COOH + (CH_3)_2C\text{=}CH_2 \rightleftharpoons CH_3COOC(CH_3)_3$$

(*c*) $$CH_3COCl + HOC_2H_5 \rightarrow CH_3COOC_2H_5 + HCl$$

$$(CH_3CO)_2O + HOC_2H_5 \rightarrow CH_3COOC_2H_5 + CH_3COOH$$

(*d*) $$CNCH_2COONa + 2C_2H_5OH + H_2SO_4 \rightarrow$$

$$CH_2(COOC_2H_5)_2 + NaNH_4SO_4$$

(*e*) $$CH_3COOH + HOC_2H_5 \rightleftharpoons CH_3COOC_2H_5 + H_2O$$
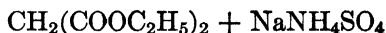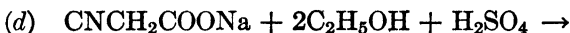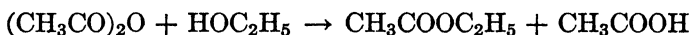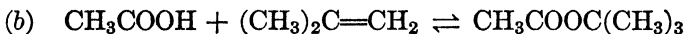
21.11   Reaction of Alkyl Halides with Salts of Organic Acids. Method *a* sometimes is used in the preparation of esters from expensive acids.   In such a case the silver rather than the sodium salt is preferred, since the former is more reactive.   Sometimes a cheaper alkylating agent, for example, dimethyl or diethyl sulfate, or an alkyl metal sulfate, replaces the more expensive alkyl halide.   Usually the reaction is carried out in a solvent, as for example alcohol, for ethyl esters.   Heating is desirable, but often not necessary.

21.12   Additions of Acids to Olefins.   In method *b* reaction takes place in the presence of a suitable catalyst, for example sulfuric acid, zinc chloride, or boron fluoride.   Ethylene is the least reactive, higher normal olefins more so, and "tertiary-base olefins," for example trimethylethylene, are most reactive.   Ethylene and propylene require temperatures of 125°, whereas trimethylethylene reacts at lower temperatures with acetic acid, when sulfuric acid is the catalyst.   Boron trifluoride is a better catalyst, causing olefins other than ethylene to react at room temperature.   The main side reaction is polymerization. This is especially pronounced with "tertiary-base olefins."

For the gas-phase reaction of isobutylene with acetic acid to form tertiary butyl acetate, ΔH from bond-energy and resonance-energy values (Tables 1–1 and 1–2) is −1.7 kcal. per mole. In the liquid phase ΔH actually is negative, since a rise in temperature causes a shift in the position of equilibrium in favor of the olefin.

21.13 Alcoholysis of Acid Chlorides and Acid Anhydrides. In method *c*, acid chlorides usually react smoothly and rapidly with primary and secondary alcohols, but abnormally with tertiary alcohols, which yield the corresponding tertiary chloride. Higher acid chlorides, for example benzoyl chloride, are much less reactive and usually require heating.

Anhydrides are less reactive than acid chlorides and usually react when heated with the alcohol. In case the alcohol is not easily acetylated (sugars for example), the addition of the fused salt of the organic acid or of zinc chloride or of a small amount of a more active catalyst [perchloric acid, sulfuric acid, hydrogen chloride (Experiment 21–2), or thionyl chloride] is desirable.

Both acid chlorides and anhydrides react more rapidly and completely with alcohols in the presence of a base. The reaction can even be carried out in the presence of water, but usually this is not desirable in the case of a highly reactive compound like acetyl chloride, because of the hydrolysis reaction. The base can be inorganic, like sodium hydroxide, or an organic tertiary amine, like pyridine. The complication from hydrolysis can be eliminated completely by using an anhydrous tertiary amine as the solvent for the reaction. In this way an alcohol can be esterified rapidly, completely, and free of side reactions such as unsaturation or isomerization. Even tertiary alcohols react satisfactorily. The reactions, especially those of acyl chlorides, are strongly exothermic.

21.14 Alcoholysis of Nitriles. In method *d*, esterification is accomplished by heating the nitrile with alcohol and sulfuric acid without the necessity of preparing the acid itself. In the case of an alkyl cyanide the first step is the formation of an imino ester, which yields the desired ester with water:

$$\text{RCN} \xrightarrow{\text{C}_2\text{H}_5\text{OH}} \underset{\overset{\|}{\text{NH}}}{\text{R—C—OC}_2\text{H}_5} \xrightarrow{\text{H}_2\text{O}} \underset{\overset{\|}{\text{O}}}{\text{R—C—OC}_2\text{H}_5}$$
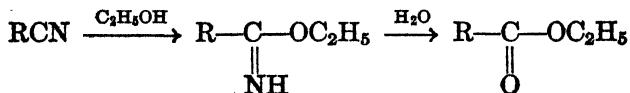
21.15 Esterification of Alcohols with Organic Acids. Method *e* is the one usually employed for the preparation of esters. This reaction, as typified in the case of ethyl acetate (Experiment 21–1) has been discussed in Chapter 1 from the standpoint of equilibrium, ΔH, and ΔF (see Section 1.2 and Subsections 1.33, 1.42, and 1.43).

The esterification of acetic acid by ethyl alcohol is a slow reaction. Even at 154° the mixture of the acid and the alcohol must be heated for more than 1 hour before equilibrium is reached. The gas-phase reaction can be catalyzed by a suitable solid contact agent of the type that catalyze dehydration reactions, as for example silica gel, which is especially effective, and aluminum oxide. The reaction then proceeds at a satisfactory rate at 150°. At this temperature the conversion of an equimolar mixture of ethyl alcohol and acetic acid is 85%, and at 200° it is 80%. The respective equilibrium constants are 33.6 and 16.0. From these data, ΔH for the gas-phase esterification is -5.8 kcal. per mole, by the van't Hoff equation (Equation 1–17). From bond and resonance energies $\Delta H = -4.0$ kcal.

In the liquid phase, esterification is markedly catalyzed by a strong proton donor, recalling the unsaturation and etherification of alcohols, and the hydration of olefins. Sulfuric acid is the usual catalyst (Experiment 21–1), although hydrogen chloride (Experiment 21–2) or an organic sulfonic acid often is used. Phosphoric acid is not so effective. Aqueous hydrochloric acid can be used for the preparation of volatile easily formed esters, for example ethyl formate, but in other cases usually it is not satisfactory. The presence of much water in the reaction mixture is undesirable, for water has two effects: (1) It decreases proton activity; (2) it promotes the reverse reaction. However, the activity of the catalyst can be raised by removing water from the reaction mixture.

Rates of reaction differ markedly, under similar conditions. The greatest effect is noted in connection with changes in the structure of the organic acid, as shown by the following order of compounds, the last one of which reacts with ca. $\frac{1}{100}$ the rate of the first:

$$HCOOH > CH_3COOH > CH_3CH_2COOH >$$

$$(CH_3)_2CHCOOH > (CH_3)_3CCOOH$$
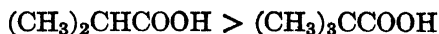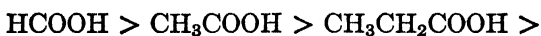
The effect of structure of the alcohol is less important, but in general the order is: Primary > secondary > tertiary. Yields with tertiary alcohols are usually low, owing chiefly to the side reaction of unsaturation. Increase in molecular weight leads to some decrease in reactivity.

The equilibrium constant in the liquid-phase reaction of any alcohol with any organic acid is essentially independent of structure and temperature. The value of the constant for the formation of ethyl acetate from equimolal mixtures of ethyl alcohol and acetic acid is 4 but varies somewhat (2.4 to 4.7) with different mixtures. However, this involves only a slight change in the percentage of conversion. The values of other equilibrium constants in general are similar.

There are three ways of driving the esterification reaction towards completion: (1) In the **simple batch process,** an excess of one reactant is present, and the mixture is heated under a reflux, if necessary, until equilibrium is reached (or in a sealed tube, in case the reaction is very slow); (2) in the **recyclization batch process,** water is continuously removed as it is formed by distilling it out as part of a two-phase distillate, and the organic part of the distillate is continuously returned to the reaction mixture; (3) in the **continuous process,** an equimolal mixture of alcohol and organic acid flows continuously into a hot reservoir containing the catalyst and some of the organic acid (or, less satisfactorily, the alcohol) while a mixture of ester, water, and some acid distils simultaneously. In the two batch processes the reaction chamber must be large enough to hold all the reaction mixture. In the continuous process a small reaction vessel may be used for a large amount of alcohol and acid.

THE SIMPLE BATCH PROCESS. This is quite general and has certain advantages, namely: (1) simple apparatus, (2) little supervision, (3) wide applicability. It has certain disadvantages, namely: (1) incomplete reaction, (2) difficulty in removing unchanged alcohol from the ester, if it is liquid, in those cases where the two cannot be separated by distillation and the alcohol is less soluble in water than in the ester, (3) side reactions leading to the formation of ether and olefin.

This process can be used in the preparation of most esters (see ethyl acetate, Experiment 21–1B) and is especially useful in the preparation of volatile esters which boil below both the alcohol and the acid, for example, methyl acetate and ethyl formate, for then the ester can be distilled over as formed. Formates may be prepared, even in the presence of much water.

THE RECYCLIZATION BATCH PROCESS. This depends on distilling out an azeotropic mixture which contains some water, removing water from the distillate, and returning the organic liquid to the reaction flask. The removal of water may be accomplished by a suitable drying agent, or more simply by causing the distillate to separate into two phases, as in the preparation of n-butyl acetate (Experiment 21–2). In this case the azeotropic mixture of n-butyl alcohol and water separates into two phases when cold. With acetates of lower alcohols the distillate may be one phase if much alcohol distils. With acetates of higher alcohols, the distillate may be one phase, due to a high acetic acid content in the distillate. However, the distillate usually can be made to separate into two phases by adding to the reaction mixture a volatile solvent which does not dissolve water, as for example carbon tetrachloride, benzene, or toluene. This modification of adding a suitable volatile solvent usu-

ally proves to be of value whenever the distillate is a single organic phase, or whenever the organic components of the reaction mixture are all so high boiling that an excessively high temperature is required for distillation.   The volatile solvent should be selected on the basis of the boiling point of the most volatile component of the reaction mixture. If, for example, ethyl alcohol (b.p. 78.4°) is the most volatile component, toluene (b.p. 110°) is not satisfactory, for very little toluene will be present in the distillate.   Carbon tetrachloride (b.p. 76.8°) is satisfactory, for the ternary azeotropic mixture contains sufficient carbon tetrachloride to produce a two-phase distillate.

The recyclization process has certain advantages, namely: (1) essentially complete esterification of the alcohol when an excess of the organic acid is taken, (2) essentially complete esterification of the acid when an excess of the alcohol is taken, and (3) wide applicability.   It has certain disadvantages, namely: (1) complicated setup, (2) some supervision.   This process is especially useful in the preparation of n-butyl and sec-butyl acetates (Experiment 21–2).

A modification of the recyclization-batch process in the case of high-boiling esters of low-boiling alcohols, for example ethyl esters of dibasic acids, comprises adding an excess of the alcohol, rapidly distilling out part of the alcohol after equilibrium has been attained so as to remove some of the water, adding another portion of alcohol, and repeating.

THE CONTINUOUS PROCESS.   This is much used for the preparation of reasonably volatile esters, for example, ethyl acetate and n-propyl acetate (Experiment 21–1A).   It has certain advantages when the reactants are run into a mixture of catalyst and organic acid, namely: (1) rapid reaction with primary alcohols, due to high concentration of catalyst and of organic acid, (2) a product essentially free of alcohol, (3) elimination of ether formation.   It has certain disadvantages, namely: (1) much supervision, (2) limitation to esters which boil well below the corresponding organic acids, (3) accumulation of water in the reaction mixture in the preparation of low-boiling esters (ethyl acetate for example), (4) olefin formation, especially with secondary alcohols, since the concentration of the catalyst is high.   Sometimes the reaction is carried out by running the mixture of alcohol and organic acid into a hot mixture of sulfuric acid and the alcohol.   The main disadvantages then are: (1) ether formation, and (2) greater tendency to olefin formation.

21.16   Side Reactions.   These are mainly unsaturation (see Chapter 14) and ether formation (see Chapter 22).   The latter sometimes is fast enough to be troublesome, especially if the reaction mixture is refluxed longer than necessary, even though the esterification reaction is the

fastest of the three.　Ether formation can be minimized by application of reaction-rate principles (Chapter 1) as in the preparation of ethyl acetate (Experiment 21–1A).

Impurities present in a reaction product, whether or not it is the equilibrium mixture, may be the unchanged acid, unchanged alcohol, water, or ether.　Acid can be removed from an ester insoluble in water by means of a suitable reaction solvent.　Sometimes the alcohol can be removed by a suitable solvent, usually water or an aqueous salt solution (Experiment 21–1B), sometimes by distillation.　But when the alcohol and ester boil close together or distil together in the form of an azeotropic mixture, naturally distillation is not effective as a method of separation.　For this reason it sometimes is desirable to keep the concentration of alcohol in the reaction mixture a minimum, as in the continuous process of preparing ethyl acetate (Experiment 21–1A).

21.17　Esters of Inorganic Acids.　These may be prepared from alcohols by the action of inorganic acids, similar to the reaction in method *e*.　Nitrous acid reacts rapidly even in dilute aqueous solution at room temperature.　The reaction is so fast and the equilibrium lies so far on the ester side that the esterification is a simple process, as in the preparation of *n*-butyl nitrite (Experiment 21–3).

$$CH_3(CH_2)_3OH + NaNO_2 + H_2SO_4 \rightarrow$$

$$CH_3(CH_2)_3ONO + NaHSO_4 + H_2O$$

Nitric acid in the concentrated form has an oxidizing action on alcohols.　This can be diminished by diluting with water, or with concentrated sulfuric acid.　The former is added when ethyl nitrate or similar volatile nitrate is prepared; the latter when the nitrate of a polyhydric alcohol, for example glycerol, is being prepared.　The reduction product of nitric acid, namely, nitrous acid, is detrimental because it rapidly reduces nitric acid to oxides of nitrogen and also forms a nitrous ester with the alcohol.　The addition of some urea or urea nitrate to the nitrating mixture is desirable, especially if a monohydric alcohol is being used, in order to destroy any nitrous acid.

Sulfuric acid and a monohydric alcohol form at room temperature an alkylsulfuric acid.　The rate is so fast that, when equal moles are mixed, equilibrium practically is reached at room temperature in 2 to 6 hours.　For the monohydric alcohols, the per cents esterified at equilibrium under these conditions lie between 53% for ethyl alcohol and 61% for methyl alcohol.

21.18　Saponification of Esters.　The hydrolysis reaction of an ester to form the respective alcohol and acid is catalyzed by hydronium

ion (from a proton donor) and by hydroxyl ion. Since in the latter case the hydroxide ion reacts with one of the products, alkaline hydrolysis, that is, saponification, goes to completion while acid hydrolysis comes to equilibrium. Saponification usually is much more rapid than acid hydrolysis; in the case of methyl acetate, the effect of hydroxyl ion is *ca.* 1300 times that of hydronium ion. Alkyl substituents in the *alpha* position of the acid and alcohol markedly decrease the rate of saponification, whereas negative radicals in the acid greatly promote the rate.

21.19 Saponification Equivalent. A valuable aid in the identification of esters is the determination of the saponification equivalent, that is, the weight of the ester, in grams, that reacts with 1 g. equivalent weight of a strong base. There are four main types of reagents: (1) aqueous sodium (or potassium) hydroxide, (2) alcoholic potassium hydroxide, (3) sodium ethoxide in absolute alcohol, (4) potassium hydroxide in diethyleneglycol (β,β'-dihydroxyethyl ether). Aqueous solutions are convenient if the ester is soluble in water. Sometimes aqueous alcohol is used. Diethyleneglycol has certain advantages, as follows: (1) It has a high-boiling point (245°); (2) it dissolves potassium hydroxide; (3) it is an excellent solvent for esters and also for fats; (4) saponification proceeds more rapidly in this solvent than in either water or alcohol, at the same temperature; and (5) the solution is stable (the titer should not change more than 0.1% in 3 months) and darkens only slowly on standing.

The solution of potassium hydroxide in diethyleneglycol is thus a generally useful reagent. It is used in Experiment 21–4, The Saponification Equivalent of an Ester.

Experiment 21–1 Preparation of Ethyl Acetate

A CONTINUOUS PROCESS (NOTE 1). Provide a 500-ml. three-necked flask with an efficient fractionating column (Note 2) attached to a condenser and with a thermometer and a glass tube (diameter 7 or 8 mm.), both reaching nearly to the bottom of the flask. The glass tube should extend 2 to 4 cm. above the stopper, for rubber connection. Attach to the glass tube, in ascending order: (1) a dropping tube (Note 3), (2) a straight glass tube 15 to 20 cm. long (Note 4) separated a distance of *ca.* 2 cm., and (3) a separatory funnel. Close the rubber tubing *above* the dropping tube with a screw clamp.

In the hood heat 175 to 200 g. of "Acetic-Sulfuric Acid Mixture for Ethyl Acetate," previously used for this preparation (Note 5), to 110°, with the bulb of the thermometer in the boiling liquid. This expels

the water which had accumulated during a previous experiment. Only in case none of the mixture is available, use a mixture of 2 moles of acetic acid and 0.5 mole of concentrated sulfuric acid. Thoroughly mix 2.0 moles of 95 or 96% ethyl alcohol (not denatured) and 2.0 moles of glacial acetic acid. Place some of this mixture in the separatory funnel, and obtain a column of liquid above the screw clamp by opening the stopcock of the funnel and forcing air up through the liquid by repeatedly squeezing the rubber tubing above the screw clamp.

With the acetic–sulfuric acid mixture in the reaction flask at 110° to 120°, run in the mixture, regulating the flow with the screw clamp at a rate equivalent to the rate of distillation of the ester. This is governed by the temperature of distillation, which should be close to the temperature of the azeotropic mixtures (Note 6). An accumulation of alcohol in the reaction mixture is undesirable since then the temperature of the reaction mixture will drop, ether may be formed, and/or the composition of the distillate will not correspond to that of the binary azeotropic mixture. The distillate should separate into two phases. After the alcohol–acid mixture has been added, continue the distillation as long as ethyl acetate distils. Do not throw away the residue, but return it to the bottle marked "Acetic–Sulfuric Acid Mixture for Ethyl Acetate."

Draw off the aqueous phase in a separatory funnel, and shake the organic liquid with dilute aqueous sodium (or potassium) carbonate until the organic phase is neutral to moist neutral litmus paper. Remove water in stages with *small* portions of a suitable drying agent (Section 12.2), and let stand overnight with more of the drying agent.

After removal of the drying agent, distil with a very small flame, collecting the fraction that distils within a 5° range near the boiling point of the ester. Calculate the percentage yield (Note 7), and label the product properly.

B SIMPLE BATCH PROCESS. In a 0.5-liter round-bottomed flask mix *thoroughly* 2 moles of ethyl alcohol, 2 moles of glacial acetic acid, and 10 g. of concentrated sulfuric acid. Remove a definite volume (1 to 5 ml.) for following the course of the reaction. Attach a reflux condenser, add some boiling aid, and heat with a flame so regulated that the liquid refluxes slowly. Follow the course of the reaction by removing a definite volume (1 to 5 ml.) of the liquid, shaking it in a small graduated cylinder with an equal volume of half-saturated aqueous sodium chloride and noting the volume of the organic phase. Do this at intervals of 5 minutes until you believe the esterification equilibrium is essentially approximated (Note 8). Keep a complete neatly tabulated record, and discontinue the heating when you think desirable.

Cool, pour the contents into about 100 ml. of *clear* half-saturated aqueous sodium chloride contained in a good-sized (about 500-ml.) separatory funnel, agitate thoroughly, and draw off the water layer. Repeat the operation three or four times with 50 to 75 ml. of this salt solution each time. Remove acetic acid from the product as described under A, and continue as in A.

Notes

1. This process may be used also for the preparation of methyl acetate, *n*-propyl acetate, and isopropyl acetate. For these, replace ethyl alcohol by an equivalent amount of the respective alcohol.

2. Similar to the one used in Experiment 16–1, The Preparation of Alkyl Bromides.

3. This is a short glass tube, about 75 mm. in length, having a dropping tip about 1 mm. in diameter ring-sealed in the center at about the middle point.

4. This may be any convenient length but need not be very long, since the pressure head required is not very great. This setup permits smooth drop-by-drop addition of one liquid to another liquid that is heated above the boiling point of the first liquid.

5. Or use a similar mixture if methyl, *n*-propyl, or isopropyl acetate is being prepared. The dark color of the mixture does not interfere with its usefulness. (*Caution:* Refer to Experiment 14–2, Note 3).

6. The azeotropic mixture of ethyl acetate and water distils at 70.5°; that of ethyl acetate, ethyl alcohol, and water at 70.3° (760 mm.). The former has the composition: ethyl acetate, 91.5%; water, 8.5%; it separates into two phases. The latter has: ethyl acetate, 83.2%; ethyl alcohol, 9.0%; water, 7.8%. This is a single-phase condensate. In this experiment there is so little alcohol in the reaction mixture that from a practical point of view the ternary azeotropic mixture is not obtained, even though it distils at the lower temperature. If it were, the distillate would not separate into two phases. A small amount of acetic acid comes over also. When preparing *n*-propyl acetate, the mixture may be heated to 130°.

7. The yield by the continuous process is 90%, and by the refluxing process, 50%.

8. Refer to the discussion on side reactions, and take this into account.

Questions

1. Why does the continuous process as here described result in a product having a lower ether and alcohol content than the refluxing process?

2. Is the crude distillate one phase or two, in the continuous process?

3. Why is it desirable to keep the distilling temperature as low as possible during the preparation by the continuous process?

4. Explain why the continuous process is not satisfactory for the preparation of *n*-butyl acetate and acetates of higher alcohols.

5. What is the function of the sulfuric acid?

6. What is the purpose of shaking with aqueous sodium chloride?

7. Could water be used instead?

8. What are the main impurities in the crude ester?

9. How were they removed?
10. What other procedures could be followed instead, for purifying the ester?
11. Why not use metallic sodium here?
12. What are the main impurities in the final products?
13. Which reagent is in excess? Why?
14. By what other methods may alcohols be esterified?
15. Compare your result with one obtained by the other method. Explain any difference.

Experiment 21–2 General Method of Preparing Esters by the Recyclization Process

n-Butyl Acetate (Note 1)

To a 500-ml. two-necked flask attach an efficient fractionating column (Note 2) carrying a thermometer. To the side arm attach a short vertical condenser (Note 3), the lower end of which drains into the open end of a liquid separator (Note 4). Connect the upper side arm of this liquid separator to a glass tube (not less than 7 mm. in diameter), which leads back, through the third neck, to the reaction flask. This tube, in the middle portion, should be bent in the form of a letter U, about 15 cm. in depth (Note 5). Fill the lower part of the separator with water up to the lower side arm. Place a graduated cylinder below the exit of the lower side arm.

Place 1.0 mole of anhydrous n-butyl alcohol (Note 6) in the flask, weigh flask and contents, and pass in dry hydrogen chloride until there is a gain in weight of 2 to 5 g., or add an equivalent amount of concentrated hydrochloric acid (Note 7). If much heat is evolved, immerse the flask in water. Add a 10 to 20% excess of *glacial* acetic acid, attach the flask to the apparatus, heat to boiling, and distil an azeotropic mixture containing water (Note 8). The distillate should separate into two phases when cooled. The lighter phase returns to the reaction flask; the heavier one flows out into the graduated cylinder. The distillation is continued until one phase only results. If the distillation is too rapid, one phase only may condense even though the reaction is not complete. Best results are obtained by regulating the heating so that the distilling temperature is not far above that of an azeotropic mixture. Toward the last, when one phase only forms, try to get a two-phase distillate by lowering the flame, so that refluxing but no distillation takes place for a few minutes, and then increasing the flame. The reaction may be considered to be complete when it is no longer possible to obtain two phases. Keep a record of the volume of the aqueous phase, which should not be less than theoretical.

Remove acid completely from the reaction mixture by shaking several times with water (refer to 6.17), and finally with aqueous sodium carbonate until the organic phase no longer tests acid to moist neutral litmus paper.   Shake again with water, and then dry in stages with small amounts of potassium carbonate (refer to 12.26).

Distil through an efficient fractionating column to remove any *n*-butyl alcohol in the form of the azeotropic mixture with *n*-butyl acetate (Note 9).   After the temperature is constant near 125°, transfer the liquid to a distilling flask, and collect *n*-butyl acetate over a 5° range near the boiling point.   Calculate the percentage yield (Note 10).

Notes

1. This process, without the addition of other solvents, is applicable to the preparation of a number of esters, namely, *n*-butyl acetate, isobutyl acetate, *sec*-butyl acetate, *n*-amyl acetate, isoamyl acetate, and *sec*-amyl acetate.   Secondary alcohols react more slowly than primary.   The process can be applied to the preparation of a large number of other esters by the addition of volatile organic liquids (see discussion).

2. The fractionating tube should be long enough to provide sufficient height for the condenser and the liquid separator.   The length of packed column, when a reflux condenser is used, should not be less than 30 cm. (refer to 9.14).

3. If a short condenser, as for example a Friedrichs condenser, is not available, a longer one may be set up in a slanting position.

4. The liquid separator is designed to separate two liquid phases and to remove them from the separator by different paths (see Figure 21–1).   The tube, *A*, should be not less than 8 mm. O.D.; otherwise, drops of water may trap some of the organic liquid.   The tube should be not less than 20 cm. in length.   The side arms should be not less than 7 mm. in diameter.

5. The liquid trapped in the U bend serves to prevent escape of vapor from the reaction flask into the separator.   If the tube is too narrow, less than 7 mm., air bubbles become

A

Fig. 21–1   Phase Separator

trapped and restrict the flow of the liquid.   Also, escape of vapor is hindered by having the tube dip under the surface of the reaction mixture.

6. If the alcohol is not anhydrous, the water collected will exceed the theoretical amount.

7. If the amount of hydrogen chloride is too great, much may be driven over, and as a result the distillate at first may not separate into two phases.   If this happens, lower the flame so as to obtain refluxing without distillation.   This allows water to accumulate.   Concentrated sulfuric acid is a good catalyst and will not distil.   Use only 1 or 2 g.   However, there is danger of charring, especially when the last of the
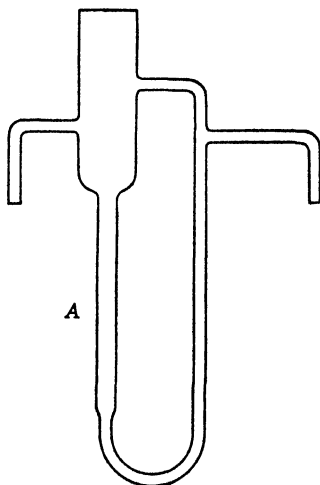
water is removed, as with a higher ester (for example n-amyl acetate). In case aqueous hydrochloric acid is added, allowance should be made for the amount of water included.

8. There are three possible azeotropic mixtures containing water: (a) the binary mixture with n-butyl alcohol (62.2% alcohol) distilling at 92.6° at 760 mm., (b) the binary mixture with n-butyl acetate (71% acetate) distilling at 90.2°, and (c) the ternary mixture with both n-butyl alcohol (27.4% alcohol) and n-butyl acetate (35.3% acetate) distilling at 89°.

9. This binary azeotropic mixture distils at 117.2° (760 mm.) and contains 53% of n-butyl acetate.

10. Yields from primary alcohols are 85 to 90%, except isobutyl. Yields from secondary alcohols and from isobutyl alcohol are 75 to 80%.

Questions

1. What is the function of the hydrogen chloride?
2. Why may only one phase condense if the distillation is too rapid?
3. What are the two different phases?
4. Does the amount of the aqueous phase correspond to the theoretical? Explain.
5. Why should the distillation temperature be close to that of an azeotropic mixture?
6. Why is acetic acid in excess?
7. Why not prepare butyl acetate in the same way as ethyl acetate in the continuous method, or in the refluxing method?
8. What is the main impurity or impurities in the crude and final product?
9. State the steps which have been taken to remove them.

Experiment 21–3   Preparation of n-Butyl Nitrite
(*Caution:* Notes 1 and 2)

In a 500-ml. beaker place about 200 g. of cracked ice, and pour onto it, with stirring (*Caution*), 1.0 mole of concentrated sulfuric acid. If the mixture is not cold, add more ice (Note 3). In a 1-liter flask (Note 4) place 0.50 mole of n-butyl alcohol, a 10% excess of sodium nitrite (Note 5), about 100 g. of water, and about 200 g. of ice. Add the cold dilute sulfuric acid, in small portions and with *vigorous* agitation, to the contents of the flask. This can be done in a few minutes, provided plenty of ice is present. If the temperature rises above 10°, add more ice (Note 6). Allow the cold reaction mixture to stand for 5 or 10 minutes, with frequent agitation, to complete the reaction.

After removing the aqueous phase, shake the organic phase two or three times with about 25 ml. of cold water (Note 7) and then with cold aqueous sodium carbonate until the organic phase is neutral to moist litmus paper (Note 8). Shake again with cold water. Finally remove water in stages by shaking with small amounts (0.5 to 1 g.) of potassium carbonate (see Chapter 12), and filter if not clear into a distilling

flask of suitable size (Note 9).   Heat with a very small flame at first, to remove water and oxides of nitrogen.   Collect the product in a 5° range (Note 11).

Notes

1. Amyl nitrite may be prepared similarly.

2. *Caution:* Organic nitrites are powerful heart stimulants, and their vapors should not be breathed. All this experiment should be carried out in the hood with a good draft. The discarded aqueous solution should be poured down the hood sink and washed down well afterward.

3. The amounts of water and ice in this experiment may be varied considerably from those given. The diluted sulfuric acid should be cold.

4. If desired, one may use a three-necked reaction flask provided with a mechanical stirrer and a dropping funnel, but, by the time the apparatus is assembled, the reaction could have been carried out.

5. The moisture content of sodium nitrite is variable and may run as high as 10%.

6. Nitrous acid begins to decompose appreciably at temperatures much above 10°.

7. These separations should be made with moderate rapidity, before the liquid becomes warm, to minimize hydrolysis.

8. The hydrolysis reaction is catalyzed by acids. The product should be neutral and dry before it is distilled.

9. The nitrite contains some *n*-butyl alcohol and water. However, it is pure enough for many purposes, if used at once.

10. It has been claimed that butyl nitrite and higher nitrites decompose when distilled at atmospheric pressure. This probably results from the observation that some oxides of nitrogen come over first.

11. Yield is 90%.

Questions

1. What conclusion can be drawn in regard to the change in solubility of sodium nitrite with temperature, from the heat effect when it dissolves?

2. How is sodium nitrite made industrially?

3. What causes the blue color during the addition of sulfuric acid?

4. What is the equation for the decomposition of nitrous acid?

5. Compare the ease of formation of *n*-butyl nitrite with that of *n*-butyl bromide and of *n*-butyl acetate.

6. What connection, if any, is there between the rate of formation of an ester and the rate of hydrolysis?

7. Write the equation for the formation of nitrosyl chloride.

8. How does it happen that one of the products is sodium bisulfate, rather than sodium sulfate?

9. What is the main impurity or impurities in the crude and final product?

10. What steps have been taken to remove them?

Experiment 21-4   Saponification Equivalent of an Ester

Into each of two 125-ml. glass-stoppered Erlenmeyer flasks transfer, by means of a suitable pipette, the tip of which has been opened to a diameter of 2 to 3 mm. (Note 1), 20 or 25 ml. of an approximately 1 N solution of potassium hydroxide in diethyleneglycol (Note 2). The two transfers should be similar in regard to time of drainage. Keep one flask for a blank, and weigh the other to within 0.01 or 0.02 g. To the latter add a suitable quantity of the ester (Notes 3 and 4), usually 1 to 5 g., replace the stopper, and again weigh (Note 5). Mix the solvent and ester by a rotatory motion of the flask and contents. *While holding the stopper firmly in place* and continually agitating the contents in the same way, apply heat slowly and gently by means of a *small* flame at such a rate that within 2 or 3 minutes the temperature of the liquid is raised to 60° or 70° (Note 6). Still holding the stopper firmly in place, shake the flask vigorously, so as to dissolve any vaporized ester. Let the liquid drain for a moment, and then cautiously loosen the stopper in order that air may escape. Replace the stopper, and continue the heating until the temperature is 120° to 130°. In the case of very high-boiling esters, the heating above 70° may be done with stopper removed, and a thermometer may be used for stirring. Heat for 3 minutes at 120° to 130° (Note 7).

Cool the flask and contents to 80 or 90°, remove the stopper, and wash it with distilled water, allowing the rinsings to drain into the flask. Dilute the contents by the addition of about 30 ml. of distilled water, add phenolphthalein, and titrate with 0.5 N hydrochloric acid. Titrate the blank, and calculate the saponification equivalent of the ester.

Notes

1. The reagent to be pipetted is very viscous.

2. This is made by weighing about 56 g. of c.p. potassium hydroxide pellets into a 500-ml. flask, adding 250 ml. of ordinary technical diethyleneglycol, and heating to effect solution while stirring with a thermometer. The temperature should not exceed 130 °C. and preferably should be kept below this; otherwise, a dark-yellow color, which is troublesome during the titration, develops. As soon as the solid has dissolved, the hot solution should be poured at once into 725 ml. of diethylenelgycol in a glass-stoppered reagent bottle, yielding approximately 1 liter of a light-yellow solution. The solution should be *mixed thoroughly* and allowed to cool. An almost colorless solution of potassium hydroxide in diethyleneglycol may be prepared by adding the potassium hydroxide to the total amount of solvent at the ordinary temperature and either shaking occasionally over a period of several days or else stirring mechanically for a few hours.

3. An unknown ester will be supplied by the instructor.

4. The amount depends on the saponification equivalent of the ester; unless it is known that the equivalent weight is high, the lower limit, that is, about 1 g., should be taken. In some cases even 1 g. is too much. The base should be in excess, about 50%.

5. Or, if convenient, weigh by difference, using a weighing pipette for liquids.

6. About the maximum temperature the hand can stand.

7. In general, the more volatile esters are the more easily saponified; by the time the stopper is first removed, the more reactive esters are completely saponified. Therefore, there should be no error due to loss of unreacted material unless the ester is both volatile and nonreactive, as for example tertiary butyl acetate. Heating for 3 minutes at 130° generally saponifies nonvolatile esters completely (for example dibutyl phthalate).

Questions

1. Why is the high-boiling point of diethyleneglycol an advantage?

2. Why does the titer of the reagent change on standing?

3. What other compounds besides esters will react with potassium hydroxide under the conditions of this experiment?

4. Why is it desirable to have a good excess of base?

5. For what ester or esters would a 1-g. sample be too large, for 20 ml. of 1 N potassium hydroxide?

Experiment 21-5   Properties of Esters

A HYDROLYSIS.   Heat 1 ml. of ethyl acetate (or butyl acetate) with 4 or 5 ml. of 70 to 80% sulfuric acid in a suitable distilling flask, the side arm of which *just* dips under the surface of neutral water in a test tube. A safety tube is attached to prevent sucking back.   After heating gently for 1 to 2 minutes, increase the heat, and distil over several drops. Test the aqueous solution for acid (Note 1).   Test it also for sulfuric and sulfurous acids.   Explain.

B SOLUBILITY.   Test the solubilities of ethyl acetate and n-butyl acetate in water, 6 N hydrochloric acid, 12 N hydrochloric acid, cold 80% sulfuric acid.

C FERRIC HYDROXAMATE TEST.   To 1 drop of ethyl acetate (n-butyl acetate or other ester) add 8 to 10 drops of 1 M methanolic hydroxylamine hydrochloride and 10 to 12 drops of 1 M methanolic potassium hydroxide to a basic reaction.   Heat just to boiling, cool, and add dilute hydrochloric acid drop by drop until acidic and then 1 to 2 drops of 1 M aqueous ferric chloride (Note 2).

Repeat, but omit the potassium hydroxide (Note 3).

Notes

1. Do this semiquantitatively with 0.01 N sodium hydroxide.

2. Esters give an intense violet (sometimes brown or wine-red) color. Some other acid derivatives will react, for example acyl halides, anhydrides, and amides. The reaction with ethyl acetate:

$$CH_3CO\!-\!OEt + HNHOH \rightarrow CH_3CO\!-\!NHOH + EtOH$$
<div align="center">acethydroxamic acid</div>

$$3CH_3CO\!-\!NHOH + FeCl_3 \rightarrow (CH_3CO\!-\!NHO)_3Fe + 3HCl$$
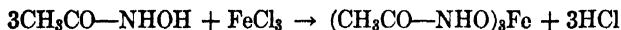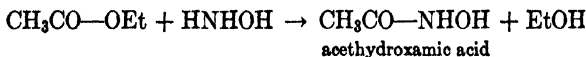
The base is added to liberate hydroxylamine from the hydrochloride, and to furnish a slight excess, for the reaction is base-catalyzed. Add more ferric chloride if the color is not intense.

3. Acyl halides and anhydrides react with hydroxylamine hydrochloride, whereas esters and amides react only with hydroxylamine, not with the hydrochloride. An ester that does not saponify readily may fail to give the test. Sometimes longer heating will lead to a positive test.

Questions

1. Name several indicators that can be used in A.

2. How were the tests for sulfuric and sulfurous acids carried out?

3. Explain the solubilities in B.

4. From the equilibrium data for the gas-phase reaction between ethyl alcohol and acetic acid, show how to calculate the value for ΔH.

Chapter 22

ETHERS

Ethers may be prepared by reactions similar to those applicable to esters, by: (*a*) the reaction of alkyl halides with the sodium salts of alcohols (the Williamson synthesis), (*b*) the addition of alcohols to olefins, (*c*) the elimination of 1 molecule of water between 2 molecules of alcohol in the gas phase, and (*d*), the same elimination in the liquid phase.

(*a*) $CH_3(CH_2)_2CH_2I + NaOC_2H_5 \longrightarrow$

$$CH_3(CH_2)_2CH_2OC_2H_5 + NaI$$

(*b*) $(CH_3)_2C{=}CH_2 + HOC_2H_5 \longrightarrow (CH_3)_3COC_2H_5$

(*c*) $C_2H_5OH + HOC_2H_5 \underset{}{\overset{KAl(SO_4)_2}{\rightleftharpoons}} C_2H_5OC_2H_5 + H_2O$

(*d*) $HOSO_2OH + C_2H_5OH \rightleftharpoons C_2H_5OSO_2OH + H_2O$

$$C_2H_5OSO_2OH + C_2H_5OH \rightleftharpoons C_2H_5OC_2H_5 + H_2SO_4$$
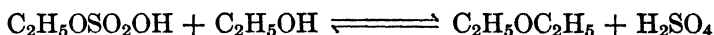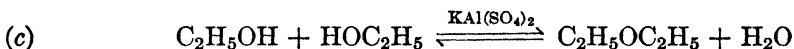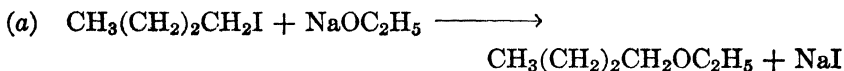
22.11 The Williamson Synthesis. Method *a* is useful in the preparation of high-molecular-weight ethers and of unsymmetrical ethers, especially mixed ethers of the aliphatic–aromatic type. In general, the rates are in the order: Iodides > bromides > chlorides. The formation of an olefin, the principal side reaction that results from the elimination of hydrogen halide from the alkyl halide, likewise is in the same order. Also, it is in the order: Tertiary > secondary > primary. In the case of tertiary halides, the olefin reaction usually predominates; of primary halides, the ether reaction usually predominates. A solution of a strong base in alcohol (alcoholic potassium hydroxide) acts much like the ethoxide. For example, a good yield of methyl *n*-butyl ether can be obtained by heating *n*-butyl bromide with a solution of potassium hydroxide in methanol (Experiment 22-3).

The preparation of an oxide, for example, 2,3-epoxybutane (Experiment 22-4) is essentially this same reaction, for the first step probably is the formation of the potassium salt of 3-chloro-2-butanol, CH₃—CH(OK)—CHCl—CH₃.

$$\begin{matrix} CH_3CHOH \\ | \\ CH_3CHCl \end{matrix} + KOH \rightarrow \begin{matrix} CH_3CH \\ | \\ CH_3CH \end{matrix}\!\!\Big\rangle O + KCl + H_2O$$
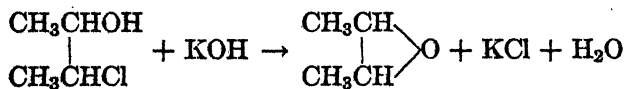
22.12   Addition of Alcohols to Olefins.   Method *b* is important industrially.   Isoamylene and other so-called "tertiary-base olefins" react more readily than other olefins.   They require a somewhat elevated temperature (60°) and the presence of a catalyst, for example sulfuric acid or an organic sulfonic acid.

22.13   Gas-Phase Ether Reaction.   In method *c*, which is important industrially owing to its economy of operation, alcohol vapor is passed over a suitable heated dehydrating catalyst, for example specially prepared aluminum oxide, aluminum sulfate, potassium alum or aluminum phosphate, in the temperature range, 250° to 300°.   The rate is higher, the higher the temperature, but, at temperatures above 300°, ethylene formation becomes important.   Only a part of the alcohol is converted to ether, owing to the fact that the system comes to equilibrium (see Thermochemistry, below).   Ether is separated from alcohol and water by fractional condensation and/or fractional distillation. The alcohol is recycled.

22.14   Liquid-Phase Ether Reaction.   Method *d* is the usual laboratory method.   Alcohol is mixed with a suitable catalyst, usually sulfuric acid, and heated until ether distils.   The additional alcohol is run in as ether distils out.   For preparing ethyl ether from ethyl alcohol, a temperature of about 140° is required for a reasonably rapid rate.   Any other strong acid would act similarly provided the temperature could be raised sufficiently.   However, few other acids perform this way.   Phosphoric acid can give the necessary temperature, but, since it is a weaker acid, it is a much less satisfactory catalyst.

The method is a "continuous" one, for a small amount of sulfuric acid theoretically can lead to the production of a large amount of ether. Practically this is not realized, since water accumulating hinders the reaction, probably because of its effect on the equilibrium and because the temperature of the reaction mixture drops.   Only a few ethers, namely, those that boil below the respective alcohols, can be prepared by the continuous process.

Higher ethers can be prepared by the recyclization process, which is so useful in the preparation of esters (Chapter 21).   The alcohol is heated with a suitable strong acid catalyst, and water is removed by distillation.

In the liquid phase, ether production takes place at a lower temperature than in the gas phase.   For ethyl ether the respective minimum temperatures are approximately 125° and 225°.   This probably is due to the fact that strong proton donors are the best catalysts.

The progress of the reaction is aided also by the presence of a siliceous earth (diatomaceous earth).   This actually may have some catalytic action or merely may aid vaporization of the ether.   An olefin is formed

if the temperature of the reaction mixture is too high.   From ethyl alcohol, ether can be obtained at 130°, ethylene at 150°.   From n-butyl alcohol, ether at about 115°, butene at 130°.   Higher alcohols react at lower temperatures than does ethyl alcohol.

Secondary alcohols do not give symmetrical ethers in good yields because of olefin formation.   It is necessary to decrease the amount of catalyst and to have more water present.   Tertiary alcohols cannot be converted into symmetrical ethers by this means.

On the other hand, a mixed ether of a tertiary and a primary alcohol, for example, ethyl *tert*-butyl ether, can be prepared by slowly distilling a mixture of the two alcohols with dilute (15%) sulfuric acid.   Likewise, a mixed tertiary–secondary ether can be prepared, using sodium hydrogen sulfate as the catalyst.   Thus, the rates with which alcohols are converted into ethers by reaction with a primary alcohol are in the order: Tertiary > secondary > primary.

22.15   Thermochemistry.   Calculation of ΔH from bond energies gives values of -5.7 kcal. for the gas-phase reaction of method b and zero for that of method c.

For method c, experimental data are available from the reaction of ethyl alcohol to form ethyl ether, in the presence of specially prepared potassium aluminum sulfate.   The equilibrium constant at one atmosphere is 7.25 at 249° and 7.69 at 266°.   The measurements were made at pressures above atmospheric in order to minimize ethylene formation.   Therefore, formation of ethyl ether is favored by a rise in temperature. From the data, calculation of ΔH using the van't Hoff equation (Equation 1–17) gives a value of 1.9 kcal., which agrees well with the value of zero, previously mentioned.   From the van't Hoff equation, and 1.9 kcal., the equilibrium constant at 25° and one atmosphere is approximately 2, by extrapolation downward.   Under these conditions, the conversion of alcohol to ether would be 60% at 25°, provided reaction would take place at this low temperature.   For n-propyl alcohol the equilibrium constant at 250° is about 11, and for n-butyl alcohol, about 14.

The nature of the heat effect in the liquid-phase reaction is difficult to approximate, because, in addition to the heats of vaporization of water, the alcohol, and the ether, their heats of solution in concentrated sulfuric acid also must be considered.

22.16   Removal of a Reaction Product.   The liquid-phase reaction is an equilibrium system similar to the gas-phase reaction and necessitates the removal of one of the products in order to obtain a satisfactory yield of ether.   The relation between the boiling points of the alcohols and those of the respective ethers is not regular, in contrast to the rather regular relation between alcohols and the respective olefins, or respec-

tive bromides, owing to the fact that the molecule of the ether has twice the number of carbon atoms that the molecule of the alcohol has. Thus ethyl ether boils well below ethyl alcohol, n-propyl ether near n-propyl alcohol, and any higher ether above the corresponding alcohol. Hence, no general procedure can be applied. The technique of removing a reaction product varies. Ethyl ether may be distilled from the reaction mixture (Experiment 22–1). For higher ethers, water is easily removed, sometimes in a separatory funnel, sometimes by distillation, as in the preparation of n-butyl ether (Experiment 22–2).

In case both the alcohol and ether are essentially nonvolatile, water can be distilled along with a volatile liquid in which water is not soluble, as for example benzene, toluene, carbon tetrachloride (see discussion, Chapter 21).

22.17 Side Reactions. In the preparation of an ether with sulfuric acid as the catalyst, the side reactions are the formation of: (1) an olefin, (2) an alkyl hydrogen sulfate, (3) an alkyl sulfate, (4) a sulfonated alcohol, and (5) sulfur dioxide along with oxidation products of the alcohol. The tendency to olefin formation is in the order: Tertiary > secondary > primary. Sulfates are formed rapidly (see Chapter 21). They are said to be intermediates in the ether reaction. Isethionic acid, $HOCH_2$-CH_2SO_3H, is slowly formed when a mixture of ethyl alcohol and sulfuric acid is heated. Sulfur dioxide results when sulfuric acid oxidizes the alcohol. This may become troublesome if the water–acid ratio is too low or if the temperature is too high.

22.18 Recovery and Purification of the Ether. If attempt is made to distil a high-boiling ether directly from the reaction mixture at atmospheric pressure, the side reactions forming olefin and sulfur dioxide may take place. Usually shaking with water removes part of the sulfuric acid and the alkyl hydrogen sulfate. Shaking with aqueous base or carbonate usually is necessary for their complete removal. Distillation usually is effective in separating the ether from unchanged alcohol, but sometimes some ether is lost, owing to the existence of an azeotropic mixture of alcohol and ether, as in the Preparation of n-Butyl Ether (Experiment 22–2). It is possible to recover the ether from such an azeotropic mixture, either by oxidizing the alcohol by alkaline permanganate or by adding water and obtaining a ternary azeotropic mixture in which the ratio of alcohol to ether is different.

Experiment 22–1   Preparation of Ethyl Ether (*Caution:* Note 1)

Provide a 500-ml. three-necked flask with thermometer, tube for inflow of liquid, and an efficient fractionating column, as in the preparation of ethyl acetate by the continuous process (Experiment 21–1A;

Notes 2 and 3).   Attach a long condenser (90 cm.).   To the condenser connect a suitable receiver provided with an exit tube to which is attached a long piece of rubber tubing extending outside a window or almost to the floor (Note 4).   The receiving flask may be surrounded by a cooling bath.

In the flask, *disconnected from the apparatus*, place 2 moles of 95 or 96%, ethyl alcohol (not denatured, Note 5), and add, with swirling and cooling under the tap, 2 moles of concentrated sulfuric acid, allowing the mixture to become warm towards the last, but not so hot that alcohol is lost by boiling.   Add 2 to 3 g. of siliceous earth (Note 6), and attach the flask to the apparatus.   Place alcohol (a part of the 2 moles below) in the funnel.   Obtain a column of liquid above the screw clamp by opening the stopcock of the funnel and forcing air up through the liquid by squeezing the rubber tubing above the screw clamp.

Bring the temperature of the liquid to 130° by means of a flame. Some ether should distil.   With the temperature of the reaction mixture at 130° to 145°, allow alcohol to flow into the reaction mixture through the dropping tube, by adjustment of the clamp, at a rate equivalent to the rate of distillation.   The rate of distillation should be governed by the temperature of distillation, which should be that of pure ether.   If alcohol is added too rapidly, part of it may distil, thus raising the temperature of distillation and increasing the difficulty of purification later, and/or it will lower the temperature of the reaction mixture, with resultant decrease in the reaction rate.   The reaction proceeds best when fine bubbles are observed throughout the liquid and the alcohol enters the solution without vigorous bumping.   Run 2 moles (Note 7) of alcohol into the reaction mixture.   This takes about 1 hour.   Continue the distillation as long as ether distils.   See that there are no flames in the vicinity before proceeding.

Shake the ether in a separatory funnel with dilute aqueous sodium hydroxide until the ether layer tests neutral to moist neutral litmus paper. (*Caution:* Release pressure quickly and several times by inverting the separatory funnel and opening the stopcock.   Be sure the stopper fits well.)   In case alcohol was not removed effectively during the distillation, shake the ether 2 to 4 times (Note 8) with an approximately equal volume of half-saturated aqueous sodium chloride.   After the last aqueous solution has settled well and been drawn off, pour the ether out of the top of the separatory funnel into a distilling flask of suitable size. Add 10 to 15 g. of finely granular or powdered anhydrous calcium chloride, and let stand for at least an hour with frequent agitation, or preferably overnight, taking proper precautions (Note 9).

Distil the ether directly from the calcium chloride by immersing the flask in water which is heated not higher than 45°.   Naturally, the dis-

tillation should be done at a proper rate and through the proper condenser. Take the necessary precautions in regard to ether vapor, and collect the part that distils within a range of 4°. Calculate the percentage yield in two ways: (1) from the weight of alcohol added through the dropping tube, and (2) from the total amount of alcohol taken (Note 10).

Label the product showing name, boiling range, weight in grams, and percentage yield.

Notes

1. *Caution:* Ether is very volatile, the vapor is very inflammable, and mixtures of ether vapor and air are explosive. In conducting this experiment be sure to have all connections air-tight and to keep flames away from the exit tube. *Caution* with sulfuric acid. (Refer to Experiment 14–2, Note 3.)

2. The apparatus may be constructed without a fractionating column, using only a distilling flask. In this case, however, the ether contains much alcohol and requires at least four washings with salt solution. The lower end of the inlet tube should then be drawn down to an opening of 1.5 to 2 mm. If it is smaller, the liquid does not flow out well; if much larger, more alcohol bubbles through unabsorbed.

3. A 50-cm. packed column used at a reflux ratio of at least 5 is effective enough to hold back the alcohol.

4. This serves to conduct the heavy ether vapor away from the flames on the desk (see Figure 7–1).

5. Commercial alcohol is 95 or 96% by volume. The amount of alcohol required in this experiment is 4 or 6 moles.

6. For example kieselguhr, Fuller's earth, or diatomaceous earth. Of the last an especially good variety is Hyflo, used in industrial filtrations.

7. Some students should run in 4 moles to observe the effect on yield.

8. In case the ether was prepared without the use of a fractionating column, it must be shaken at least four times with the salt solution.

9. A vessel containing cold ether should not be closed too tightly with a well-fitting stopper, because the extra pressure resulting from warming to room temperature may cause the flask to break.

10. The yield on the basis of total alcohol is 55%.

Questions

1. Compare yields on the basis of 4 moles and 6 moles of alcohol used, both on the basis of alcohol run in and of total alcohol taken.

2. Why is the ether shaken with sodium hydroxide solution?

3. What is the source of the impurity that is removed?

4. Why is ether shaken with sodium chloride solution? Could water be used instead?

5. What remains in the reaction flask after the end of the experiment?

6. What reaction would take place if this were heated to a higher temperature?

7. Write equations for other reactions by which ethyl ether may be prepared.

8. In case methanol were present in the ethyl alcohol (as in some denatured alcohols), what compound or compounds might be present in the ethyl ether?

9. What do you predict to be the better combination of reactants in the Williamson synthesis of ethyl *tert*-butyl ether?

10. What is the relationship between the boiling points of normal primary alcohols and the respective ethers? Explain.

11. In the gas-phase production of ether from alcohol, how does high pressure minimize olefin formation?

12. Calculate ΔH for ether formation in the vapor phase from equilibrium data.

13. What are the main impurities in the crude and final products?

14. What steps have been taken to eliminate them?

Experiment 22-2   Preparation of Di-*n*-Butyl Ether (*n*-Butyl Ether)

Provide a 500-ml. three-necked flask with a thermometer which will record the temperature of the vapor. Attach also, as in Experiment 21-2, the Preparation of *n*-Butyl Acetate, an efficient fractionating column (Note 1) and a phase separator, for separating the two-phase distillate and returning the organic phase to the boiler.

In the flask, which is disconnected from the apparatus for this purpose, add slowly with *thorough* mixing 0.3 to 0.5 mole of concentrated sulfuric acid to 3 moles of anhydrous *n*-butyl alcohol (Notes 2 and 3). Attach the flask to the apparatus, heat to boiling, and distil an azeotropic mixture containing water (Note 4). The distillate should separate into two phases when cooled. The lighter phase returns to the reaction flask, and the heavier one flows into the graduated cylinder. Continue the heating, which requires 4 or 5 hours (Note 5), until almost 2 moles of water have been collected (Note 6), or until the temperature in the reaction flask reaches the boiling point of *n*-butyl ether (Note 7).

Remove the acid from the reaction mixture by shaking several times with water and finally with aqueous sodium hydroxide, until the organic phase no longer tests acid to moist neutral litmus paper. After washing about twice with water, dry with a small amount of a suitable drying agent (Note 8).

Through an efficient fractionating column remove the binary azeotropic mixture of *n*-butyl alcohol and *n*-butyl ether (Note 9). After all the alcohol has distilled, and the temperature has reached *ca.* 140°, transfer the liquid to a distilling flask (Note 10), and collect the butyl ether over a 5° range near the boiling point (Note 11).

In order to recover ether from the binary mixture, add water, and redistil to obtain the ternary azeotropic mixture, in which the ether-alcohol ratio is greater (Note 12). Dry, and distil as before. Calculate the percentage yield (Note 13).

Notes

1. The fractionating tube should be long enough to provide sufficient height for the condenser and the liquid separator. The length of packed column, when a reflux condenser is used, should not be less than 30 cm.

2. When more sulfuric acid is present, unsaturation of the alcohol may take place before the ether reaction is complete. When 1 mole of acid is present, unsaturation sometimes starts at 130°. Considerable darkening occurs with 0.5 mole of acid.

3. Do not add boiling chips or any other solid substance which may promote the formation of olefin.

4. There are three possible azeotropic mixtures containing water: (a) the binary mixture with n-butyl alcohol (62.2% alcohol) distilling at 92.6° at 760 mm., (b) the binary mixture with n-butyl ether (67% ether) distilling at 93°, and (c) the ternary mixture with both n-butyl alcohol (42.9% alcohol) and n-butyl ether (27.7% ether), distilling at 91°.

5. The operation may be interrupted at any time without significantly affecting the yield.

6. Some water is formed in the reaction of sulfuric acid with the alcohol to form sulfuric esters.

7. Some butene may be formed as the final temperature is approached.

8. Refer to Tables 12-2 and 12-3 and also Subsections 12.26 and 12.28.

9. This binary azeotropic mixture distils at 117.25° (760 mm.), and contains 12% ether. If the reaction has been carried out properly, the amount of this binary mixture should not exceed 10 g.

10. The column and flask can be rinsed out with a very volatile solvent, as for example ethyl ether. The solvent can be removed by distilling *slowly* with a small flame.

11. Di-n-butyl sulfate, if present, may undergo decomposition toward the end of the distillation.

12. In an alternative procedure, the alcohol is oxidized by refluxing with water, potassium permanganate, and potassium hydroxide, and the ether is recovered by steam distillation. It must be dried and distilled.

13. Yield is 70%.

Questions

1. Could di-n-butyl ether be prepared by a continuous process, as in the case of ethyl ether?

2. What are advantages and/or disadvantages of using a larger or a smaller amount of sulfuric acid?

3. What compound or compounds may be formed when sulfuric acid is heated with n-butyl alcohol at 100°? at 150°?

4. What compound or compounds may be formed between sulfuric and n-butyl ether at 20°? at 150°?

5. Do you think the reaction to form n-butyl ether is reversible? Explain.

6. Which of the three azeotropic mixtures containing water distils at the beginning, middle, and end of the process?

7. What are disadvantages of removing the alcohol by heating with aqueous alkaline permanganate?

8. What factors cause the yield to be low?

9. Evaluate the relative importance of these.

10. If you were asked to prepare *n*-butyl ether by some other method, how would you proceed?

11. What are the impurities in the crude and final products?

12. What steps were taken to remove them?

Experiment 22–3   Preparation of Methyl *n*-Butyl Ether

Equip a 1-liter three-necked flask with a sealed mechanical stirrer, a thermometer reaching nearly to the bottom of the flask, a reflux condenser, and a dropping funnel (Note 1). In the flask dissolve 0.8 to 1.0 mole of potassium hydroxide (Note 2) in a suitable volume of 90% methanol (by volume, Notes 3 and 4) with agitation. With the temperature of the liquid at 50° to 55°, slowly run in 0.5 mole of *n*-butyl bromide with agitation at a rate such that the heat of reaction causes an even reflux. The *n*-butyl bromide may be added at a faster rate if external cooling is applied. However, the temperature should not drop below 50° (Note 5). In case the temperature drops below 50°, apply heat with a very small flame. As more solid separates, increase the rate of stirring (Note 6). After all the butyl bromide has been added, maintain at refluxing temperature until the reaction seems to be complete (Note 7), and continue for 0.5 to 1 hour longer (Note 8). Add 100 to 150 ml. of water (Note 9 and Question 12). Attach an efficient fractionating column at least 40 cm., preferably 60 cm. in length, and distil the ternary azeotrope of water, methanol, and methyl *n*-butyl ether until the boiling point of methanol is reached (Notes 10 and 11). Remove methanol from the distillate by several washings with cold water (7 or 8 ml.) or with cold sodium chloride solution (Note 12). Remove any dissolved water by means of a suitable drying agent (Note 13), and distil, collecting in a 5° range near the boiling point of the ether. Calculate the percentage yield. Label the product, showing boiling point and percentage yield (Note 14).

Notes

1. For sealed mechanical stirrers refer to 15.17. The dropping funnel can drain into the top of the condenser.

2. Technical flakes are satisfactory. Other ethers may be prepared using primary alcohols and primary alkyl bromides (or iodides). Methanol is the most reactive of the alcohols in this type of reaction.

3. At least 100 ml. of solvent should be used. A larger volume of solvent permits better agitation and will not complicate recovery of the product, in case the latter is separated in the form of the ternary azeotropic mixture.

4. The alcohol should contain *ca.* 10% water. The presence of some water is desirable, for then (*a*) the reaction is much more rapid; (*b*) the potassium bromide which forms crystallizes out in a definite crystalline form, rather than in a fine state of subdivision; and (*c*) less butene is formed.

5. The formation of butene usually increases if the temperature rises.

6. There is little danger of the flask breaking so long as the solid is kept in good agitation. The stirring should become more vigorous as the volume of the ether phase increases.

7. The course of the reaction may be followed thus: Remove a definite volume of the upper liquid phase (2 ml. is sufficient), add plenty of water, and steam-distil slowly with a small flame, collecting the two-phase distillate in a test tube.

By means of a dropper remove the organic phase, add to this an equal volume of methanol (to furnish hydrogen for the reduction) and then a small cube of metallic sodium. (*Caution:* It may be necessary to cool, if the reaction is vigorous.) After the sodium has reacted, add water cautiously, remove the organic phase (to be returned to the reaction mixture), acidify the aqueous phase with c.p. nitric acid, and add aqueous silver nitrate in excess. Set the tube aside, repeat at regular intervals (15 or 20 minutes), and compare the different results. Usually after about 2 hours of refluxing the test shows that little or no butyl bromide is present.

8. The yield is better if the mixture is heated longer or if it stands for several days. The yield is 90% after the mixture has stood 3 weeks.

9. The distillation proceeds more smoothly if the salt is dissolved.

10. Refer to 9.14 and 9.15. The ternary azeotropic mixture boils at 56°.

11. In an alternative procedure the reaction mixture is diluted with water, and the organic phase is separated in a separatory funnel. The recovery of ether is lower in this case, owing to the relatively large volume of methanol.

12. The ether is somewhat soluble in water at room temperature, more soluble at elevated temperature and less soluble in salt solution.

13. Refer to Tables 12–2 and 12–3, and Subsections 12.26 and 12.28, Drying Capacity and Removal of Drying Agent.

14. Methyl *n*-butyl ether boils at 70.3°. The yield is 70%.

Questions

1. How does the presence of potassium hydroxide lead to the formation of methyl *n*-butyl ether?

2. What is the reaction that results in the formation of butene?

3. How can this reaction be minimized?

4. How can it be made more important, so as to give a good yield of butene?

5. Why is distillation of the ternary azeotropic mixture continued beyond 57–58°?

6. Why does not the addition of more methanol and/or more water adversely affect the recovery of the ether when it is distilled out in the form of the ternary azeotropic mixture?

7. Would this be true if the reaction product were poured into water instead of being distilled? Explain.

8. Why should the stirring become more vigorous as the volume of the ether phase increases?

9. When testing for unreacted butyl bromide, why not take a sample of the lower phase?

10. When testing for unreacted butyl bromide, why is steam distillation employed?
11. What is the function of metallic sodium in this test?
12. What is the solubility of potassium bromide in water at 25°; at 60°?
13. What impurity or impurities do the crude and final products contain?
14. What steps have been taken to remove them?

Experiment 22–4 Preparation of 2,3-Epoxybutane

β-Butylene Oxide (Note 1)

In a 2-liter round-bottomed flask provided with a thermometer extending past the middle of the flask, a sealed mechanical stirrer (refer to Chapter 15), a dropping funnel, and a short wide bent tube leading to a downward condenser, dissolve 14 to 15 moles of potassium hydroxide (Note 2) in 1 liter of water. Slowly add during vigorous agitation, while the solution is maintained at 90°, 3.5 moles of 3-chloro-2-butanol (β-butylene chlorohydrin, Experiment 19–5; Note 3). About 2 hours is required. After all of the chlorohydrin has been added and distillation has ceased, some additional oxide may be recovered by steam distillation, merely by raising the temperature (Note 4).

Dry the liquid with anhydrous potassium carbonate (Note 5), and filter if not clear. Distil slowly up to 50° with a small (micro-) flame, collecting the fraction separately. Remove water, which causes the boiling point to be low, by means of potassium carbonate, as before. Add the dried liquid to the flask. Collect the 50° to 60° fraction (Note 6). Yield is 87 to 90%. Label the product properly.

Notes

1. An epoxy compound is a cyclic ether.
2. The technical product, preferably flakes or pellets, is satisfactory. Although the amount specified is a large excess, the reaction proceeds so much more smoothly throughout than when the excess is not large that the procedure is justified.
3. Solid potassium chloride soon begins to settle out.
4. The hot alkaline solution should be removed from the flask without needless delay since it slowly etches glass.
5. Anhydrous calcium chloride must not be used, as it forms a solid addition product with the higher boiling oxide. Refer to 12.28 in regard to drying in stages with potassium carbonate as a drying agent.
6. Boiling points are: cis-2,3-epoxybutane, 60.5°; trans-2,3-epoxybutane, 54°.

Questions

1. Which general method of ether production does this reaction resemble?
2. What other compound might be used in place of 3-chloro-2-butanol for preparing this oxide?

3. Do you think that sodium hydroxide would work as well as potassium hydroxide? Explain.

4. Why not dry the product with calcium chloride?

5. Why is the product collected over such a wide range?

6. How many butylene oxides (epoxybutanes having three-membered rings) are possible?

7. How many amylene oxides (epoxypentantes having three-membered rings) are possible?

8. What impurity or impurities do the crude and final products contain?

9. What steps have been taken to remove them?

Chapter 23

ACID CHLORIDES

Acid chlorides may be prepared in the laboratory from organic acids or from their salts by the action of: (a) inorganic acid chlorides, or (b) organic acid chlorides:

(a) $\qquad$ $PCl_5 + CH_3COOH \rightarrow CH_3COCl + POCl_3 + HCl$

$$PCl_5 + CH_3COONa \rightarrow CH_3COCl + POCl_3 + NaCl$$

$$POCl_3 + 3CH_3COONa \rightarrow 3CH_3COCl + Na_3PO_4$$

$$PCl_3 + 3CH_3COOH \rightarrow 3CH_3COCl + P(OH)_3$$

$$SOCl_2 + CH_3COOH \rightarrow CH_3COCl + SO_2 + HCl$$

$$SOCl_2 + CH_3COONa \rightarrow CH_3COCl + SO_2 + NaCl$$

(b) $\qquad$ $C_6H_5COCl + CH_3COOH \rightleftharpoons CH_3COCl + C_6H_5COOH$
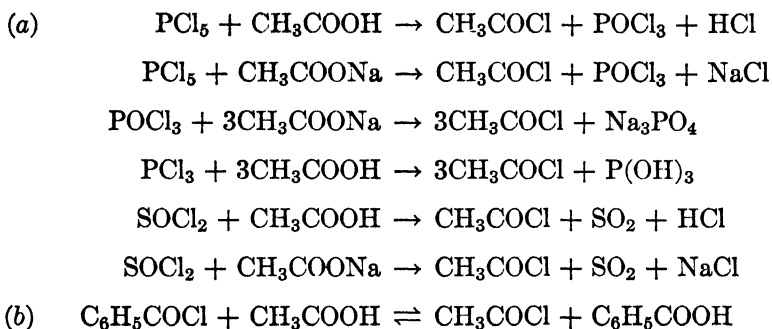
23.11 Inorganic Acid Chlorides. In method a the commonly used inorganic acid chlorides, in decreasing order of reactivity, are phosphorus pentachloride (sublimes at 160°), phosphorus trichloride (b.p. 76°), and thionyl chloride (b.p. 79°). Phosphorus pentachloride reacts vigorously with acids without heating, and the reaction is strongly exothermic. The trichloride sometimes requires heating, and the heat effect is small. Thionyl chloride usually requires heating. The reaction is endothermic. The reaction of all three with salts of organic acids is much faster and more strongly exothermic than with the acids themselves. The choice of reagent to be used depends in part on its boiling point and the boiling points of the reaction products.

Phosphorus pentachloride works best for acid chlorides boiling above 180° or for those boiling below about 90°, since phosphorus oxychloride, the other product of the reaction, boils at 107°. Acid chlorides that react only slowly with cold water, as for example aromatic sulfonyl chlorides, often can be isolated by adding the reaction mixture to ice, for the phosphorus chlorides are decomposed while the organic acid chloride is not altered much.

Phosphorus trichloride works well for acetyl chloride (Experiment 23–1) and a few other volatile acid chlorides. It can be used for less

volatile acid chlorides by employing reduced pressure for distilling the desired product away from phosphorous acid, which, though not volatile, decomposes when heated much above 150°, yielding a variety of products, including phosphine. Sometimes the desired product can be decanted from the phosphorous acid, since usually the reaction mixture consists of two liquid phases, of limited solubility in each other.

A disadvantage in the use of chlorides of phosphorus is the tendency to form mixed anhydride–acid chlorides, in which one or more of the chlorine atoms is replaced by an acyl radical, as for example RCOO—PCl_2, $(RCOO)_2PCl$, and $(RCOO)_3P$. In the case of phosphorus trichloride this leads to the formation of hydrogen chloride.

$$PCl_3 + CH_3COOH \rightarrow CH_3COO—PCl_2 + HCl$$
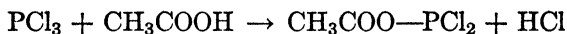
Thionyl chloride although it is the least reactive is superior in that usually there are no side reactions and the inorganic reaction products are gaseous. However, the gaseous nature of the other products is a disadvantage if the acyl chloride is quite volatile, as for example acetyl chloride, for then much of it is carried away in the gas stream. Thionyl chloride is especially useful for high-boiling acid chlorides. The reaction can be followed by the rate of gas evolution.

The advantages of using the salt of the organic acid, rather than the acid are: (1) nonvolatility of the resulting inorganic salt, (2) greater reactivity, (3) greater yield, in the case of phosphorus pentachloride, (4) no complication from gaseous hydrogen halide. Principal disadvantages are: (1) the heterogeneous nature of the reaction mixture, and (2) the strongly exothermic nature of the reaction.

23.12 Organic Acid Chlorides. In method *b* benzoyl chloride (b.p. 198°) is very useful because it has a high-boiling point and is readily available. Usually the yields are 70 to 90%. The reaction is of the equilibrium type and is driven to completion by the distillation of the lowest-boiling component, which is the desired acyl chloride, as fast as it is formed. A side reaction which is not very extensive is anhydride formation (Chapter 24), resulting in the evolution of some hydrogen chloride.

Experiment 23–1   General Method of Preparing Acyl Chlorides

Acetyl Chloride (Note 1)

Set up a distilling apparatus, thoroughly *dry*, using 200-ml. distilling flasks for both boiler and receiver. To the boiler attach a dropping funnel, and to the receiver attach a calcium chloride tube, to protect

from moisture.   To this attach a device by which the evolved hydrogen chloride, along with any acetyl chloride and phosphorus trichloride, will be completely absorbed in water, without danger of water sucking back (Notes 2 and 3).   Agitation later is easier if the boiler, condenser, and receiver are attached to a single movable stand.

Put 1 mole of *glacial* acetic acid in the boiler, and surround it by cold water.   In a well-ventilated hood transfer 90% of the theoretical amount of phosphorus trichloride (sp. gr. 1.6) to the dropping funnel.   With thorough mixing (swirling) add the phosphorus trichloride in a small stream.   Replace the cold water by water at 40° to 50°, and, following the slackening in the evolution of hydrogen chloride (Note 4) and the separating of the liquid into two layers, gradually raise the temperature of the bath to boiling.   Distil as long as liquid comes over (Note 5).

Redistil through a dry condenser into another dry flask as before, at first very slowly with a microflame, to drive out hydrogen chloride. Collect the fraction which distils in a 5° range near the boiling point of acetyl chloride.   Calculate the percentage yield (Note 6).   Use part of the product for Experiment 23–2, and turn in the remainder to the instructor when reporting the experiment.

Notes

1. For acyl chlorides boiling much above 100° the distilling temperature must be lowered by reduced pressure.
2. A satisfactory arrangement is a large bottle, at least 1-liter in capacity, closed with a grooved one-hole stopper carrying a glass tube leading about to the middle. The bottle is about one third full of water.
3. The vapors of both phosphorus trichloride and acetyl chloride are harmful to breathe; on that account they must not be allowed to escape into the laboratory. All transfers should be made in a well-ventilated hood, with *dry* vessels.   The apparatus should be washed out under the hood, and all washings should be poured down the sink in the hood.
4. Hydrogen chloride is formed as the result of side reactions (refer to 23.11).
5. Because phosphorous acid decomposes, it is better not to use a flame.
6. Yield is 60%.

Questions

1. Why must the apparatus be dry?
2. Explain why the water in the bottle is efficient, even though the tube does not touch the water.
3. Why should the vessel have plenty of air space?
4. Why should the tube not dip under the surface of water?
5. Which reagent is in excess, and why?
6. What impurities does the acetyl chloride contain?
7. How may the impurities be removed?

8. Why is it better not to use a flame?

9. Why not use phosphorus pentachloride in place of phosphorus trichloride?

10. Why does the acetyl chloride on redistillation begin to distil below the boiling point of pure acetyl chloride?

11. Aside from side reactions, what causes the yield of pure acetyl chloride to be low?

12. What modifications would be desirable for the preparation of valeryl chloride? Propionyl chloride?

13. What reaction leads to the formation of hydrogen chloride?

Experiment 23–2   Properties of Acid Chlorides

A SOLUBILITY. Cautiously add 4 to 5 drops of acetyl chloride to 2 ml. of ice water. Are the liquids miscible? Shake carefully. Repeat with benzoyl chloride.

B ESTER FORMATION. (*Caution:* The reaction that takes place is violent. Perform the experiment in the hood.) Cautiously add 1 ml. of acetyl chloride to 1 ml. of ethyl alcohol, which is kept cold during the process. Describe what happens. Add the product to an equal volume of cold half-saturated aqueous sodium chloride. Note the separation of an organic liquid and its characteristic odor.

C AMIDE FORMATION. (*Caution:* See above.) To 5 drops of aniline in a centrifuge tube add, drop by drop from a dropper with cooling, 5 or 6 drops of acetyl chloride. Mix thoroughly by means of a thin rod, breaking up the cake of solid. Add a little cold water (*ca.* 2 ml.), shake, centrifuge, decant off the water, and repeat twice (Note 1). Dissolve the residue in hot water (*ca.* 2 ml.; Note 2), filter (while hot) by taking the liquid into a dropper, the end of which is plugged with cotton. Transfer the liquid quickly to a second centrifuge tube, and cool. Collect the solid by centrifuging, dry it on porous plate, and take the melting point (Note 3). Save this product for Experiment 24–3.

D FERRIC HYDROXAMATE TEST. Repeat Experiment 21–5C, but replace the ester with an acyl halide.

Notes

1. Removal of most of the acid is necessary before heating the solid with water; otherwise, it undergoes hydrolysis.

2. If heat is applied at the end of the centrifuge tube, the contents are liable to be expelled by bumping. Use a microflame, and apply heat above the end of the tube.

3. The product is acetanilide $CH_3CONHC_6H_5$. This type of reaction is of value in the identification of acid chlorides (or acids after conversion to the chloride) and of amines, since both can be converted to solids and the melting point determined. To be of value, the solid derivatives of different compounds must not melt too close to each other.

Questions

1. What are the equations for the reactions in A, B, C, and D?
2. Compare the reactivities of the compounds in A.
3. With what types of organic compounds does acetyl chloride react?
4. Calculate ΔH values for the reactions in A, B, and C.
5. Calculate ΔH values for the reactions used in the preparation of acid chlorides by method a.
6. How do you explain the difference in the results in D and in Experiment 21–5C?

Chapter 24

ACID ANHYDRIDES

Acid anhydrides of organic acids may be prepared from the organic acids by the action of: (a) inorganic acid anhydrides, (b) organic acid anhydrides, and from salts of the acids by the action of: (c) organic acid halides, (d) inorganic acid halides.

(a) $2CH_3COOH + P_2O_5 \rightarrow CH_3CO—O—COCH_3 + 2HPO_3$

(b) $C_2H_5COOH + (CH_3CO)_2O \rightleftharpoons$

$$C_2H_5CO—O—COCH_3 + CH_3COOH$$

$$C_2H_5CO—O—COCH_3 + C_2H_5COOH \rightleftharpoons$$

$$C_2H_5CO—O—COC_2H_5 + CH_3COOH$$

(c) $CH_3COONa + CH_3COCl \rightarrow CH_3CO—O—COCH_3 + NaCl$

(d) $2CH_3COONa + SOCl_2 \rightarrow$

$$CH_3CO—O—COCH_3 + 2NaCl + SO_2$$
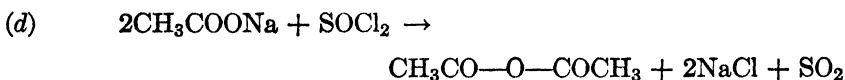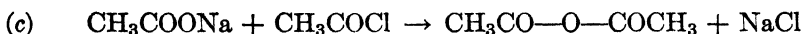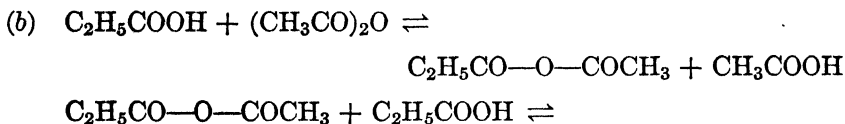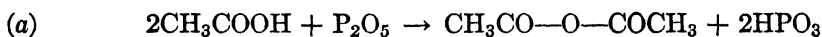
24.11 Inorganic Anhydrides and Organic Acids. In method a anhydrides that react exothermically with water, that is, anhydrides of moderately strong acids, such as phosphorus pentoxide and sulfur trioxide, react with acids. Since the yields are not good, the method is not used much.

24.12 Organic Anhydrides and Organic Acids. In method b the equilibrium which exists between the two acids, as for example acetic and propionic acids, CH_3COOH and C_2H_5COOH, and the three possible anhydrides $(CH_3CO)_2O$, $(C_2H_5CO)_2O$, and $CH_3CO—O—COC_2H_5$ involves merely an exchange reaction between acyl groups. Naturally, the heat effect is essentially zero. The reaction is catalyzed by a strong acid, for example hydrogen chloride or hydrogen sulfate. The reactions can be driven to the right by removing the acetic acid through distillation, for it is the most volatile of the compounds present. The product may be the mixed (unsymmetrical) anhydride of the two acids, or the symmetrical anhydride of the higher acid, depending on the ratio of reactants. One reactant usually is acetic anhydride because it is the cheapest anhydride and also because acetic acid (except for formic acid) is the most volatile of the acids.

Anhydrides of dibasic acids are similarly prepared. These are linear polymers except in the case of succinic acid, glutaric acid, and their derivatives. These form cyclic anhydrides of five- and six-membered rings. In Experiment 24–2, d-α-β-diacetoxysuccinic anhydride is prepared by the action of acetic anhydride on d-tartaric acid. The hydroxyl groups are esterified in the process of anhydride formation.

$$\begin{array}{l} \text{HO—CH—COOH} \\ \quad | \qquad\qquad\quad + 3(CH_3CO)_2O \rightarrow \\ \text{HO—CH—COOH} \end{array}$$

$$\begin{array}{l} \text{CH}_3\text{COO—CH—CO} \\ \qquad\qquad | \qquad\qquad >\!\!O + 4CH_3COOH \\ \text{CH}_3\text{COO—CH—CO} \end{array}$$
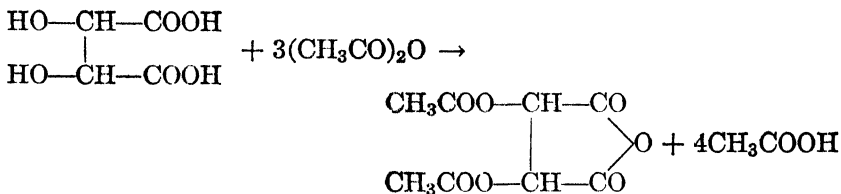
24.13 Organic Acid Halides and Salts of Organic Acids. In method c the acid halide is heated with the anhydrous finely pulverized salt. This is the usual method and is followed in Experiment 24–1, The Preparation of Acetic Anhydride. A disadvantage is the heterogeneous nature of the reaction mixture, including also the formation of a metallic halide which protects the salt of the organic acid. The rate is low on this account. Acid chlorides are commonly used, mainly because bromides and iodides are expensive. The product may be either a symmetrical or an unsymmetrical anhydride, depending on whether the acyl radical of the acid chloride is the same as or different from the acyl radical of the salt.

24.14 Inorganic Acid Halides and Salts of Organic Acids. In method d the first step may be considered to be the formation of the organic acid chloride (Chapter 23), which then reacts with more of the salt to produce the anhydride as shown in c. Usually the reaction is strongly exothermic and, even though heterogeneous, may require careful control. Other inorganic acid chlorides besides thionyl chloride that may be used are phosphorus oxychloride, sulfuryl chloride, or sulfur chloride. Some of these are important industrially. Also, the acids, rather than the salts, often may be converted into anhydrides by inorganic chlorides.

Experiment 24–1   General Method of Preparing Acid Anhydrides

Acetic Anhydride

Attach a dry reflux condenser to the neck of a 200-ml. dry distilling flask, incline the apparatus so that the side arm drains into the flask, and close it by means of a cork stopper with a hole bored half way

through (Note 1). To the top of the condenser fit a calcium chloride drying tube. In an iron vessel (crucible or dish) freshly fuse enough sodium acetate so that you will have about $\frac{2}{3}$ mole of the freshly fused salt (Note 2). Rapidly grind it to a *very fine powder*, weigh it, and put it into the distilling flask. In a well-ventilated hood (Note 3), add in portions, shaking well after each addition, 0.5 mole of acetyl chloride (Notes 4 and 5). Shake well, attach to the condenser, and heat the flask until the acetyl chloride has reacted (Note 6).

Remove the bath, change the position of the condenser for distilling (or use a second, dry condenser for that purpose), and use as a receiver a dry 125-ml. distilling flask, protected from the air by a calcium chloride tube. Heat the flask by means of a small luminous flame, which is held in the hand and kept constantly in motion, or heat by means of an oil bath (Note 7). Gradually increase the intensity of heating. Continue the heating as long as any liquid distils. Add 5 grams of powdered fused sodium acetate to the distillate, let stand for some time with frequent agitation, and distil again into a dry weighed bottle, collecting over a 5° distilling range. Calculate the percentage yield (Note 8). Label the product, showing boiling point and yield.

Notes

1. Or a round-bottomed flask may be used. In this case the distillate is driven over through a bent tube fitted to the top of the flask.

2. Securely fasten the vessel between two iron rings, one below, the other above. Stir continuously while the fused salt solidifies. Note that the salt slowly decomposes above its melting point. Refer to Experiment 13–1, Note 2.

3. The vapors of acetyl chloride and acetic anhydride are harmful to breathe. On that account they must not be allowed to evaporate into the laboratory. All transfers should be made in a well-ventilated hood, in dry vessels. The apparatus should be washed out under the hood, and all washings should be poured down the sink in the hood.

4. The material prepared in Experiment 23–1 is satisfactory.

5. Thionyl chloride or other inorganic acid chloride may replace acetyl chloride, but the molal ratios will be different. Since the reaction is strongly exothermic, the chloride should be added gradually from a dropping funnel, and the exit gases, after passing through a reflux condenser, should be run into a suitable absorbing train (see Experiment 23–1). A two-necked or three-necked flask is recommended so that the contents of the flask can be mixed at intervals. Also, the temperature of the vapor can be ascertained.

6. Bumping is less if an oil or wax bath at 100° is used, instead of a flame. However, a luminous sooty flame usually is satisfactory. A steam bath or boiling-water bath can be used, but then there is danger that water may come in contact with the product. The progress of the reaction can be followed by noting the temperature of refluxing.

7. Refer to 7.15, Bumping Due to Solids.

8. Yield is 75%.

Questions

1. Why must the apparatus be dry?
2. Which reagent is in excess, and why?
3. How can you be sure that all of the acetyl chloride has reacted?
4. Why is the sodium acetate added when the product is redistilled?
5. What is the heat of the reaction in this experiment?
6. What are the main impurity or impurities in the crude and final products?
7. What steps have been taken to remove them?

Experiment 24–2   Preparation of d-Tartaric Anhydride Diacetate

To 0.1 mole of finely ground d-tartaric acid (Note 1) in a suitable flask (200 ml.) add a 25% excess (Note 2) of freshly distilled acetic anhydride (Note 3) and 4 to 5 drops of concentrated sulfuric acid (Note 4). Mix well with a gentle whirling motion, so as not to deposit the solid acid on the upper part of the flask. Swirl the contents continuously. The mixture should warm spontaneously. Maintain at 50° to 60° by occasional cooling until the reaction slackens (Note 5), and then apply gentle heating. Continue until all the acid has dissolved, warming finally to 80° to 90°. Maintain at 80° to 90° for 10 to 15 minutes with exclusion of moisture (Note 6).

Allow to cool to about 60°, and initiate crystallization by scratching or seeding (Note 7). Let cool slowly to promote formation of large crystals, and let stand overnight. Collect by suction filtration with minimum exposure to air (Note 8). After no more liquid passes through, even when well pressed, break suction, and wash two or three times with 10-ml. portions of anhydrous benzene C_6H_6 (Note 9). Remove residual benzene and acetic acid in a clean dry vacuum desiccator containing paraffin chips and solid sodium hydroxide in separate vessels. Determine melting point and yield of the solvent-free solid (Note 10).

Notes

1. Crystalline d-tartaric acid has no water of crystallization. Crystalline racemic and meso-tartaric acids are monohydrates. They can be converted to the corresponding anhydride diacetates, but more acetic anhydride should be taken. If the acid is not in finely divided condition, reaction is much slower.

2. The equation for the reaction must be considered in order to make the calculation. A 50% excess may be taken, but the yield is less.

3. Acetic anhydride is liable to deteriorate in a glass-stoppered bottle.

4. Hydrogen chloride is not so good a catalyst as sulfuric acid. More must be taken. However, it has the advantage that darkening is less likely.

5. If the temperature should rise to about 70°, then on cooling to 50° the tartaric acid crystals become larger and thus are more difficult to bring into solution later.

6. At higher temperatures decarboxylation as well as darkening may take place.

7. The anhydride has a pronounced tendency to supersaturate. If crystallization is not initiated, the mixture may stand for several days without crystallizing. If crystallization is initiated at or near room temperature the solid is finely crystalline.

8. The compound should not come in contact with moisture. In order to prevent exposure to air, the best technique is the use of a rubber dam over the solid.

9. This removes acetic acid, but not tartaric acid, if any should remain. For that reason no tartaric acid should be left unreacted. The anhydride is somewhat soluble in acetic acid and more so in acetic anhydride.

10. The melting point of the pure compound is 132.5–133°. The usual yield is 85%. As prepared this way a melting point of 129–130° is satisfactory.

Questions

1. Why does acetic anhydride deteriorate in a glass-stoppered vessel?

2. How many moles of acetic anhydride react with 1 mole of tartaric acid to form tartaric anhydride diacetate?

3. What is formed when tartaric acid undergoes decarboxylation?

4. What two types of reaction does tartaric acid undergo in this experiment?

5. How can the reversible reaction between succinic acid and acetic anhydride be driven to completion, from the standpoint of succinic acid?

6. Why do the tartaric acid crystals become larger when the temperature drops from 70° to 50°?

7. Why should not the product come in contact with moisture?

Experiment 24–3   Properties of Acetic Anhydride

A   ACETIC ANHYDRIDE AND WATER.   Add 1 to 2 ml. of the anhydride to 4 to 5 ml. of water, and shake thoroughly. Do they mix? Warm gently. Compare with the action of acetyl chloride and water.

B   ACETIC ANHYDRIDE AND ALCOHOL.   (*Caution:* The reaction that takes place in this experiment is likely to be violent. Perform the experiment under the hood.) Put 1 ml. of absolute alcohol and 1 ml. of acetic anhydride in a test tube. Do they mix? Is there evidence of action? Support the tube in a vertical position by means of a clamp. Transfer one drop of concentrated sulfuric acid to the mixture by means of a thin glass rod. Describe the results. Add the liquid, after reaction, to an equal volume of cold half-saturated aqueous sodium chloride. Note the odor. In case the odor of the anhydride persists, add 6 N sodium hydroxide with cooling, until slightly alkaline.

C   ACETIC ANHYDRIDE AND AN AMINE.   (*Caution:* See above.) Add 2 ml. of the anhydride to 2 ml. of aniline, and heat. While still hot pour the product into 10 ml. of cold water in a test tube, shake vigor-

ously, decant off the water, and shake twice more with 10 ml. of cold water, decanting each time. This is done to remove acetic acid. Add the solid to 10 ml. of boiling water, boil for 1 minute, filter quickly while hot through a fluted filter paper, and cool the filtrate in running water. Filter off the crystals by suction, dry them on a porous plate, and determine the melting point (Notes 1 and 2). Take a melting point of a mixture of this product and the product from Experiment 23–2C.

D FERRIC HYDROXAMATE TEST. Repeat Experiment 21–5C, but replace the ester with an anhydride (Note 3).

Notes

1. The product is acetanilide. (See Experiment 23–2, Notes 1 and 3.)
2. This experiment may be performed with semimicro amounts, as in Experiment 23–2.
3. In case a negative result was obtained with the anhydride in the absence of potassium hydroxide, repeat, first heating a drop of the anhydride with a drop of alcohol (preferably n-butyl alcohol on account of lower volatility than ethyl). The resulting ester should react as in Experiment 21–5C, first half.

Questions

1. What are the equations for the reactions in A, B, C, and D?
2. What is the value of the reactions typified by B and C?
3. With what types of organic compounds does acetic anhydride react?
4. Which is the more reactive, acetic anhydride or acetyl chloride? Discuss from rate of reaction point of view.
5. Why is it desirable to remove acetic acid in C?
6. How do you explain the difference in the results in D and in Experiment 21–5C?
7. Calculate the approximate value of ΔH for the liquid-phase reactions in A, B, and C.

Chapter 25

KETONES AND ALDEHYDES

Ketones can be prepared by: (*a*) the pyrolysis of calcium or barium salts of carboxylic acids, (*b*) the pyrolysis of carboxylic acids, (*c*) the catalytic dehydrogenation of secondary alcohols, (*d*) the oxidation of secondary alcohols, (*e*) the hydration of alkynes, (*f*) syntheses with Grignard reagents, (*g*) syntheses with acetoacetic ester (see Chapter 40).

(*a*) $CH_3CH_2COOCaOCOCH_2CH_3 \rightarrow CH_3CH_2COCH_2CH_3 + CaCO_3$

$\underset{\rule{2.5cm}{0.4pt}}{CH_2CH_2COOCaOCOCH_2CH_2} \rightarrow \underset{\rule{2cm}{0.4pt}}{CH_2CH_2COCH_2CH_2} + CaCO_3$

(*b*) $CH_3CH_2COOH + HOCOCH_2CH_3 \rightarrow$

$$CH_3CH_2COCH_2CH_3 + CO_2 + H_2O$$

(*c*) $CH_3CH_2CHOHCH_3 \rightleftharpoons CH_3CH_2COCH_3 + H_2$

(*d*) $5H_2SO_4 + Na_2Cr_2O_7 + 3C_2H_5CHOHCH_3 \rightarrow$

$$3CH_3CH_2COCH_3 + Cr_2(SO_4)_3 + 2NaHSO_4 + 7H_2O$$

(*e*) $H_2O + CH_3C\equiv CCH_3 \rightarrow CH_3CH_2COCH_3$

(*f*) $CH_3CH_2C\equiv N + BrMgCH_2CH_3 \rightarrow$

$$CH_3CH_2C(=NMgBr)CH_2CH_3$$

$$H_2O + 2HCl + CH_3CH_2C(=NMgBr)CH_2CH_3 \rightarrow$$

$$CH_3CH_2COCH_2CH_3 + MgBrCl + NH_4Cl$$

$$CO_2 + 2BrMgCH_2CH_3 \rightarrow (CH_3CH_2)_2C(OMgBr)_2$$

$$H_2O + (CH_3CH_2)_2C(OMgBr)_2 \rightarrow (CH_3CH_2)_2CO + 2BrMgOH$$

Aldehydes can be prepared in even more ways, as follows, of which *a, b, c, d, e,* and *f* are special cases of the ketone synthesis: (*a*) the pyrolysis of a mixture of the calcium (or barium) salts of formic acid and a carboxylic acid, (*b*) the pyrolysis of a mixture of formic acid and a carboxylic acid, (*c*) the catalytic dehydrogenation of a primary alcohol, (*d*) the oxidation of a primary alcohol, (*e*) the hydration of acetylene (for

acetaldehyde alone), (*f*) the reaction of Grignard reagents with ethyl orthoformate, (*h*) the reduction of acid derivatives, the Stephen reduction of nitriles, and the Rosenmund–Kuhn hydrogenolysis of acid chlorides, (*i*) the depolymerization of polymers; (*j*) the ozonolysis of unsaturated compounds.

(*a*) $(C_2H_5COO)_2Ca + Ca(OCHO)_2 \rightarrow 2CH_3CH_2CHO + 2CaCO_3$

(*b*) $C_2H_5COOH + HOCHO \rightarrow CH_3CH_2CHO + CO_2 + H_2O$

(*c*) $CH_3CH_2CH_2OH \rightleftharpoons CH_3CH_2CHO + H_2$

(*d*) $[O] + CH_3CH_2CH_2OH \rightarrow CH_3CH_2CHO + H_2O$

(*e*) $H_2O + HC\equiv CH \rightarrow CH_3CHO$

(*f*) $HC(OEt)_3 + BrMgCH_2CH_3 \rightarrow HC(OEt)_2CH_2CH_3 + BrMgOEt$

   $H_2O + HC(OEt)_2CH_2CH_3 \rightarrow CH_3CH_2CHO + 2EtOH$

(*h*) $HCl + CH_3(CH_2)_6C\equiv N \rightarrow CH_3(CH_2)_6CCl\!=\!NH$

$4HCl + 2SnCl_2 + 2CH_3(CH_2)_6CCl\!=\!NH \rightarrow$

$(CH_3(CH_2)_6CH\!=\!NH\cdot HCl)_2SnCl_4 + SnCl_4$

$H_2O + (CH_3(CH_2)_6CH\!=\!NH\cdot HCl)_2SnCl_2 \rightarrow$

$2CH_3(CH_2)_6CHO + 2NH_4Cl + SnCl_4$

$H_2 + CH_3(CH_2)_6COCl \rightarrow CH_3(CH_2)_6CHO + HCl$

(*i*) $(CH_3CHO)_3 \rightarrow 3CH_3CHO$

(*j*) $Zn + H_2O + CH_3CH\!-\!O\!-\!CHCH_3 \rightarrow 2CH_3CHO + Zn(OH)_2$
$\underset{\textstyle \rule{2.5cm}{0pt}}{\quad\;\; \underline{\quad\; O_2 \quad}}$

25.11 Pyrolysis of Salts of Carboxylic Acids. In method *a* a symmetrical ketone is obtained when the calcium or barium salt of the acid is heated, as in the preparation of acetone from calcium acetate (Experiment 25–1). An unsymmetrical ketone can be prepared by heating a mixture of the salts of two acids, and an aldehyde is obtained when one of the acids is formic acid. The salt mixture is prepared by evaporating a solution of the two salts. Naturally the formation of calcium carbonate can take place in three ways when two salts are present with the result that a mixture of three ketones is obtained in the one case and a mixture of one ketone and the aldehyde in the other case. Actually yields of aldehydes are poor.

Salts of the dibasic adipic and pimelic acids give good yields of the cyclic ketones, cyclopentanone and cyclohexanone, respectively. The

yields of larger-ring ketones drop off rapidly as the separation of the carboxyl groups increases. Best yields of larger-ring ketones result from cerium and thorium salts. Even under best conditions, only about 1% of cyclododecanone is formed from the C_{13} dibasic acid. The yields are somewhat better with the C_{15} ketone.

25.12 Pyrolysis of Carboxylic Acids. In method *b* the acid is decarboxylated catalytically by passing the vapors over thorium oxide at 400°, with yields of 70 to 90%. Other catalysts are manganese oxide, titanium oxide, iron oxide, cerium oxide, calcium carbonate, and barium carbonate. Manganese oxide and titanium oxide usually are more satisfactory than thorium oxide, for with these the reaction can be carried out at a lower temperature. The process probably involves the formation of the salt of the metal, followed by its decomposition into the ketone and the oxide or carbonate of the metal. The metal compound then forms the salt with another portion of the acid.

An unsymmetrical ketone is obtained, along with the symmetrical ketones, from a mixture of two fatty acids, but, if one of the acids is formic acid, an aldehyde is formed. At 250° to 300° over titanium oxide, the yield of aldehyde sometimes is as high as 50%. This is in marked contrast with the results from the pyrolysis of calcium or barium salts which gives poor yields. Cyclic ketones result from dibasic acids. For cyclopentanone and cyclohexanone, merely heating the high-boiling dibasic acid with a small amount of the catalyst is sufficient to bring about ketone formation, as in Experiment 25–2, The Preparation of Cyclopentanone. The decarboxylation reaction is endothermic.

25.13 Catalytic Dehydrogenation of Alcohols. In method *c* an alcohol is dehydrogenated by passage of the vapor at a temperature of 200° to 350° or even higher, over a suitable catalyst such as metallic copper, or, better, an alloy of copper, such as copper–zinc. For example, isopropyl alcohol is dehydrogenated over metallic copper slowly at 150°, rapidly at 250° to 430°. The system approaches an equilibrium as discussed below. The resulting mixture is cooled, and unchanged alcohol is separated from the aldehyde or ketone by distillation and is recycled. This method is important industrially.

Calculation from bond energies shows that ΔH for the gas-phase dehydrogenation of primary alcohols is approximately +15 kcal. and of secondary alcohols, +12 kcal. It is evident that a reaction to form a ketone is more exothermic (or less endothermic) by 3 kcal. than a similar reaction to form an aldehyde. The reason is that the bond energy of the C=O group is greater by 3 kcal. in the case of a ketone (152 kcal., versus 149 kcal.). Thus, at room temperature both reactions, if they could be made to take place, would be endothermic.

Because of the magnitude of ΔH, it is reasonable to predict that at room temperature ΔF of dehydrogenation is positive.   From the values for the free energies of formation of ethyl alcohol and acetaldehyde, namely, -42 and -32 kcal. respectively, ΔF of dehydrogenation is $+10$ kcal. Therefore, the equilibrium, which is known to exist in this system, lies well over on the alcohol side and is shifted to the aldehyde side by a decrease in the pressure, or by a rise in temperature.   However, the limiting temperatures are determined by the onset of side reactions, such as dehydration of the alcohol, or decomposition of the aldehyde. Some catalysts permit higher temperatures than others.   Thus, metallic rhenium at $400°$ gives an 85% yield of acetone without the formation of propylene.

25.14   Oxidation of Alcohols.   In method d oxidation can be carried out in the gas phase with oxygen (or air) over catalysts similar to those mentioned under c.   This method is sometimes used commercially.   The reaction is exothermic, for the hydrogen, which would be formed by dehydrogenation, is converted to water in the oxidation reaction.   For calculating ΔH, therefore, the heat of formation of 1 mole of water vapor, namely, 58.3 kcal., must be subtracted from the ΔH values above.   Thus in the gas-phase oxidation of an aldehyde, ΔH is approximately -43 kcal., and of a ketone -46 kcal.   The important problem here is the control of the reaction temperature.

Oxidation of alcohols ordinarily is carried out in the laboratory as a liquid-phase oxidation by **chromic acid mixture,** that is, an aqueous solution of potassium (or sodium) dichromate and sulfuric acid.   The rate with which oxidation takes place is dependent on the ratio of sulfuric acid to water.   Satisfactory acid concentrations are usually in the range 4 to 8 M, as in the preparation of butanone (Experiment 25–3). If the concentration is too high, the desired product is oxidized.   Naturally at the lower concentration more time must be allowed, or the temperature must be raised.   But at higher temperatures undesirable side reactions are more extensive.   One of these probably is the oxidation of the ketone.   When an aldehyde is being prepared, its removal as soon as formed is necessary; otherwise, oxidation to the corresponding acid will take place.   Oxidation with dichromate is exothermic to the extent of 60 to 70 kcal. per mole of aldehyde produced.   Because of the strongly exothermic nature of this reaction, control is necessary by the slow addition of one reactant accompanied by temperature control, as in Experiment 25–3, the Preparation of Butanone.

25.15   Hydration of Alkynes.   In method e acetylene or a homolog reacts with water at room temperature or higher in the presence of a suitable catalyst, consisting of an acid and a mercury salt, usually

sulfuric acid and mercuric sulfate. Acetylene yields acetaldehyde; a monosubstituted acetylene, as for example 1-propyne, yields a ketone rather than an aldehyde; a symmetrical alkyne, as for example 2-butyne, yields a single ketone; and an unsymmetrical alkyne, as 2-pentyne, yields two ketones. Sometimes it is sufficient to dissolve the acetylenic compound in sulfuric acid and dilute with water as in the case of phenyl-propiolic acid $C_6H_5C{\equiv}CCOOH$, which is converted into benzoylacetic acid $C_6H_5COCH_2COOH$.

From bond-energy values ΔH of hydration of a monosubstituted or disubstituted acetylene is -46 kcal. The reaction is sufficiently exothermic to expect no reversal of the reaction at room temperature.

25.16   The Grignard Synthesis. In method f, Grignard reagents add to nitriles, RCH_2CN, acid chlorides, and esters. The resulting addition compounds with nitriles, namely, ketimine magnesium halides, on hydrolysis under acid condition, yield the ketones. Side reactions to form other products, especially hydrocarbons, cut down yields considerably, especially in some cases with acetonitrile. In the case of acid chlorides and esters, the reaction may continue, with the formation of tertiary alcohols.

The reaction of Grignard reagents with carbon dioxide can be controlled to yield ketones rather than acids (Chapter 20) by heating and by keeping the Grignard reagent in excess.

25.17   Acetoacetic Ester Synthesis. In method g ketones are obtained by the ketonic scission of derivatives of acetoacetic ester (Chapter 40); these are monosubstituted and disubstituted acetones, RCH_2COCH_3 and $R_2CHCOCH_3$, respectively.

25.18   Reduction of Acid Derivatives to Aldehydes. Nitriles are reduced by first converting them with anhydrous hydrogen chloride in ether solution to nitrilium chlorides and then adding anhydrous stannous chloride. The resulting imino addition compounds yield aldehydes on the addition of water.

Hydrogenolysis of acid chlorides to aldehydes is carried out catalytically by passing hydrogen gas into a boiling xylene solution of the acid chloride in the presence of metallic palladium on barium sulfate. The barium sulfate lowers the activity of the catalyst to such an extent that the aldehyde is not reduced readily. The progress of the reduction is followed by determining the amount of hydrogen chloride evolved.

Hydrogenolysis of acid chlorides is only moderately exothermic ($\Delta H = -17$ kcal.). Since the $T\Delta S$ term of Equation 1–29 in this case is not large (same number of reactants and products), ΔF for the hypothetical gas-phase reaction has a large negative value. Consequently, the reverse reaction probably is not significant. As actually carried

out, one of the reaction products, namely, hydrogen chloride, is continually removed, and this further eliminates the reverse reaction. The method is useful for higher aldehydes.

25.19   Depolymerization of Polymeric Forms. Method i is useful in the preparation of formaldehyde and acetaldehyde by heating paraformaldehyde and paraldehyde, respectively. In the former case it is merely sufficient to heat the solid polymer, but, unless moisture has been removed, the formaldehyde repolymerizes on cooling. Pure paraldehyde depolymerizes so slowly that it can be distilled unchanged at atmospheric pressure (125°). However, the rate of depolymerization is so increased by the presence of a strong acid, that acetaldehyde can be distilled from the boiling liquid (Experiment 25–4), in spite of the fact that the equilibrium lies well over on the side of the polymer. Since ΔH of polymerization is -12.6 kcal., the equilibrium at lower temperatures favors the polymer still more. Thus, the presence of a trace of acid in liquid acetaldehyde causes rapid and practically complete conversion to paraldehyde. For this reason a nonvolatile acid, for example an organic sulfonic acid, is preferred. Sulfuric acid, although it is often used, is inferior for it has an oxidizing action. The resulting sulfur dioxide distils with the product.

25.195   Ozonolysis. In method j ozone is passed into a solution of the olefin in some solvent, usually carbon tetrachloride or ethyl acetate. The ozonide is decomposed by water in the presence of zinc dust. Ozonides are explosive, especially when dried. Only small amounts are prepared at one time. A symmetrical olefin, for example 2-butene, yields a single aldehyde, whereas an unsymmetrical olefin, such as 2-pentene, yields a mixture of two aldehydes.

Experiment 25–1   General Method of Preparing Ketones

Acetone (Note 1)

Weigh into a large Pyrex test-tube, preferably 200 x 40 mm., calcium (or barium) acetate (Note 2) until the tube is about two-thirds full (Note 3). Close it with a tightly fitting stopper carrying a piece of glass tubing not less than 6 mm. inside diameter, and attach this to a condenser. To the lower end of the condenser attach an adapter which should drain into a small (30- to 60-ml.) flask, placed close up to minimize evaporation losses. By means of an iron clamp (Note 4) fix the test tube in an essentially horizontal position, so that all parts of it can be brought into the flame by rotation, but slanted slightly so that any liquid that condenses will not run back on the heated portions.

Heat with a luminous flame from a fishtail burner, and rotate the tube frequently to minimize overheating (Note 5).   Heat until distillation ceases.

Put the condensate into a small separatory funnel, and remove as *much of the water as possible in stages* with potassium carbonate (Note 6). Distil from a suitable flask in contact with additional potassium carbonate, heating either with water at 60° to 70° or with a microflame. Collect in a weighed flask the material that distils up to 60° (Note 7).   In case much liquid remains undistilled, collect higher-boiling material, in cuts, and subject this to systematic fractional distillation (refer to 9.13).

Notes

1. This procedure serves for the preparation of many ketones (see discussion). The apparatus must be modified for high-boiling ketones, so that they are not pyrolyzed. This may be prevented by heating with a bath, or by reducing the pressure, or by both.

2. It is recommended that this be dried in an oven at 110°.

3. Considerable free space is desirable so that the solid will not pack but can be kept loose by rotating the tube.

4. Castaloy may melt.

5. Overheating causes excessive charring.   Some slight charring takes place slowly, in any event.

6. The more completely water is removed at this point, the less is the loss of product when distilled (refer to 12.26 and 12.28).

7. The yield varies, owing in part to variations in the amount of water in the calcium acetate.   From the anhydrous salt the yield is about 70%.

Questions

1. What is the formula of crystalline calcium acetate?

2. Explain the source of the water in the distillate.

3. What drying agents are preferable to potassium carbonate in the final distillation?

4. How else may acetone be prepared?

5. From probability considerations alone, what would be the ratio of ketones from the pyrolysis of an equimolar mixture of calcium acetate and calcium propionate?

6. If diethyl ketone were being prepared, should the final distillation be done from potassium carbonate?

7. What is the main impurity or impurities in the crude and final product?

8. State the steps that have been taken to remove them.

Experiment 25–2   Preparation of Cyclopentanone

Equip a 300-ml. distilling flask (Note 1) with a thermometer reaching to within 1 or 2 mm. of the bottom, and attach a condenser for distillation (Note 2).   Place 0.40 mole of adipic acid and 0.04 mole of man-

ganese carbonate in the flask (Notes 3 and 4). Heat carefully with a small flame set rather close to the flask, and if necessary agitate the flask, in order to shake the solid into the melted acid. When the acid is entirely melted, increase the rate of heating until the thermometer registers 280°, at which temperature decomposition should take place. Maintain the temperature at 280° to 290° (Note 5) as long as a liquid distils (Note 6). If the distillate is collected directly in a 60-ml. short-stem separatory funnel, loss due to transfer is cut down (Note 7).

To the two-phase distillate in a separatory funnel add sufficient solid potassium carbonate to saturate or nearly saturate the aqueous phase. At first add only small amounts, a gram or less, making sure that any acid is neutralized. Finally, draw off the aqueous phase, and remove water in stages with additional potassium carbonate (Section 12.2). Filter the ketone if not clear into a distilling flask of suitable size, and distil, collecting over a 2° or 3° range near the boiling point of cyclopentanone. Calculate the percentage yield (Note 8), and label the product.

Notes

1. It may be better but it is not necessary to use a flask that permits the use of a short column (1 or 2 cm.) of glass rings, as for example a flask with two openings or one with a Claisen neck. The advantage of the short column in returning adipic acid is counterbalanced by the greater difficulty in distilling. A long column is neither necessary nor desirable.

2. If the experiment is to be carried out on a large scale, one may use a three-necked reaction flask and pass the vapor through a short distilling tube (6 to 8 cm.) holding a short column of glass rings (2 to 4 cm.).

3. Although desirable, it is not necessary that the solids be mixed beforehand. However, the acid should go into the flask first; otherwise, reaction between the two later may be slow.

4. Of the various metallic oxides and carbonates that form easily decomposable salts of adipic acid, manganese carbonate is one of the best.

5. If the temperature rises above 290°, adipic acid begins to distil, and at 295° a dense white smoke fills the apparatus. Under these conditions, more adipic acid will be carried over. It is better to keep the temperature at all times below 290° in order to avoid the delay entailed in allowing the mixture to cool and in readjusting the flame, in case the liquid becomes too hot.

6. When the reaction is at an end, a dense white fog is suddenly evolved.

7. The residue in the distilling flask is difficult to remove. Let it stand overnight with some alcohol to which some solid sodium hydroxide has been added.

8. Yield is 75–80%.

Questions

1. What other product or products can be formed by decarboxylation of adipic acid under these conditions?

2. What condition is responsible for the presence of a fog during the first distillation?

3. Do you think it possible to avoid the production of fog in this experiment?

4. Why is a long fractionating column unnecessary and undesirable?

5. How may cyclopentanone be obtained from (a) other acyclic compound? (b) cyclic compound? Write equations.

6. What is meant by acyclic?

7. What is the main impurity or impurities in the crude and final product?

8. State the steps taken to remove them.

Experiment 25–3   Preparation of Butanone
(Methyl Ethyl Ketone)

In a 1-liter round-bottomed flask, preferably a long-necked flask, add 1.9 moles of sulfuric acid, while agitating and cooling in a stream of water from the tap, to 200 to 400 ml. of water (Note 1). To the cool mixture add 1.0 mole of 2-butanol (Note 2), and place a thermometer in the flask. In a separate small flask, dissolve a 5% excess of sodium dichromate (Note 3) in 50 ml. of water. Put the reaction flask in an ice bath, and, while swirling vigorously, add the dichromate solution in small portions of 5 to 10 ml. at a time. Reaction takes place immediately, shown by the change in color. Keep the temperature of the reaction mixture between 20° and 40° (Note 4). When the reaction is over (Note 5), add 50 to 100 ml. of water, connect the flask to a suitable fractionating column, and distil out the ketone (Note 6) into a weighed flask.

Dry the distillate with potassium carbonate (Note 7), filter if not clear, and distil from a suitable flask, collecting a 3° fraction near the boiling point of the ketone (Note 8). Calculate the percentage yield of the ketone (Note 9).

Notes

1. If the sulfuric acid is too concentrated, that is, if it is diluted with much less than 200 ml. of water, the reaction is difficult to control, and side reactions become more prominent. If it is too dilute, that is, if the amount of water is over 400 ml., the reaction is so slow that much butanol may remain unoxidized unless the reaction mixture is heated for a while after all the dichromate has been added. When oxidizing sec-amyl alcohol to pentanone by this method, more water should be present, about 500 ml., on account of the lower solubility. Longer heating is necessary.

2. In order to be sure of the amount of 2-butanol, either determine the density, or test for water by shaking with a small amount of potassium carbonate. The density D_4^{20} is 0.8063 for the anhydrous alcohol, and 0.8620 for the azeotropic mixture with water, which boils at 87.5° (760 mm.).

3. Before making the calculation, find out if the available dichromate is the dihydrate (the usual form) or the anhydrous.

4. When the lower limit of water is used, that is, 200 ml., the temperature of the reaction mixture should be kept below 20° during the first half of the oxidation. If the temperature is too high, the yield is diminished, probably because the ketone is attacked.

5. When the mixture, *at room temperature* and out of the ice bath, is shaken for 5 to 10 minutes without any rise in temperature, the reaction is essentially complete. However, at the higher dilution, let stand for some time, or preferably warm to about 50°.

6. The azeotrope of butanone with water boils at 73.5° and contains 11.9% water by weight. The distillation should be stopped before the temperature reaches 87°, in the event a sharp break in the temperature is not observed.

7. Approximately 9 g. of the carbonate will be required, and so 6 g. may be added at once and shaken until it dissolves completely in the water layer formed, which is then drawn off. The drying is completed in stages by addition of more potassium carbonate (refer to 12.26 and 12.28).

8. If the ketone is not water-white but has a yellow tinge, biacetyl may be present. This can be removed by distillation if two or three small flakes of sodium hydroxide are added first.

9. Usual yield is 80 to 85%.

Questions

1. What other organic compounds besides the ketone and biacetyl might be formed during the oxidation of the alcohol?

2. What would happen to any other such products, and at what part of the procedure will they be removed from the ketone?

3. Approximate the composition of the first distillate from your data, and compare it with the data in Note 6. Explain any discrepancy.

4. What is the formula of biacetyl?

5. How do you account for the presence of biacetyl?

6. Why is sodium dichromate used, rather than potassium dichromate? Could potassium dichromate be used?

7. For the purpose of oxidizing 2-butanol to butanone, how does alkaline permanganate compare with dichromate and sulfuric acid?

8. Write equations showing how butanone may be obtained from other compounds besides 2-butanol.

9. What are the probable impurities in the crude and final products?

10. State the steps taken to remove them.

Experiment 25–4   Preparation of Acetaldehyde

To a 100- or 200-ml. round-bottomed flask attach a suitable packed fractionating column (Note 1). Connect a *long* condenser cooled by ice water, and attach a 100-ml. weighed (with stopper) conical flask as receiver (Note 2) by means of a long stem adapter which reaches well into the flask (Note 3). Attach a tube to prevent entrance of moisture, and cool the receiver in ice (Note 4).

Place in the reaction flask 0.2 mole of paraldehyde and 1 to 2 g. of benzenesulfonic acid or *p*-toluenesulfonic acid (Note 5). Heat with a *very small* flame, and carry on a slow distillation so that the distilling temperature does not exceed 30°. After the reaction is over, weigh the receiving flask, and calculate the percentage yield (Note 6).

Make up an aqueous solution of aldehyde, and at the same time note the extent of miscibility of the two liquids by adding 1 ml. of acetaldehyde to 1 ml. of ice water in a 10-ml. graduate. Then add more ice water to bring the volume to 10 ml. Use this solution in Experiment 25–5 for making tests (Note 7).

Notes

1. The minimum packed column, when a cold-finger condenser cooled by ice water is used, is about 20 cm. in length.

2. The receiver may be a flask with two outlets, for example a small suction flask or distilling flask.

3. Connection is facilitated if the lower part of the adapter is straight and of uniform diameter.

4. The aldehyde must be anhydrous if it is to be used in a Grignard synthesis (see Experiment 19–4).

5. Or add 4 or 5 drops of 75 to 80% sulfuric acid.

6. The yield is essentially quantitative.

7. Acetaldehyde is more stable in this solution than in the pure state, and moreover it is not so easily lost by evaporation. If kept in a moderately well-stoppered vessel, the solution is satisfactory, even after several days.

Questions

1. Should the fractionating column be more efficient than in Experiment 16–1, or will a less efficient one suffice?

2. Did the thermometer at the top of the column record the boiling point of acetaldehyde? Explain.

3. What is the function of the sulfonic acid?

4. In what way is a sulfonic acid superior to sulfuric acid?

5. Discuss what effect on the yield of acetaldehyde, if any, the length of packing in the column has.

6. Suppose one drop of cold 80% sulfuric acid is added to separate 10-g. portions of acetaldehyde and paraldehyde at 0°, what reactions take place? Is there any difference in the rates?

7. Explain why evaporation of acetaldehyde is less after water has been added.

8. Explain why acetaldehyde is more stable in the presence of water than in the pure state.

9. By what process may acetaldehyde be obtained from ethyl alcohol?

10. By what process may acetaldehyde be obtained from acetylene?

11. What is the main impurity or impurities in the product?

Experiment 25–5   Properties of Ketones and Aldehydes

A   ADDITION REACTIONS

1. Sodium Bisulfite. Shake 5 ml. of acetone with 10 ml. of a freshly saturated solution of sodium bisulfite (Note 1). Let stand for several minutes. Test the crystals for solubility in water.

Repeat with butanone.

B   CONDENSATION REACTIONS

1. Aldehyde Resin. Heat about 2 ml. of the acetaldehyde solution (Experiment 25–4) with about 5 ml. of sodium hydroxide solution. Note any change. Repeat with a ketone.

C   OXIDATION OF ALDEHYDES AND KETONES

1. Permanganate, Neutral and Alkaline. To a few drops of the acetaldehyde solution add 1 or 2 drops of aqueous potassium permanganate. Repeat the test with dilute (about 10%) solutions of pure acetone and butanone. In case no action is observed after about 1 minute, add a few drops of aqueous sodium carbonate.

2. Permanganate, Acid. Repeat above, but with permanganate acidified with dilute sulfuric acid.

3. Fehling's Solution. To 10 ml. of solution resulting from mixing 5 ml. each of Fehling's Solutions I and II (Note 2) add 2 or 3 drops of the acetaldehyde solution. Boil gently for 2 or 3 minutes. Repeat with a ketone.

4. Tollen's Reagent. Clean a test tube or small beaker thoroughly by heating gently with concentrated nitric acid (*Caution*), rinsing with aqueous sodium hydroxide and water. Place in the vessel 4 or 5 ml. of Tollen's reagent (Note 3) and a few drops of a quite dilute formaldehyde solution (Note 4). Repeat with acetaldehyde solution and with a ketone.

5. Iodoform Test. Perform the iodoform test (Experiment 19–6G) using, in place of alcohol: formaldehyde, acetaldehyde, acetone, butanone, and cyclopentanone.

6. Nitric Acid. Hood. Heat 2 or 3 drops of cyclohexanone with *ca.* 1 ml. of 6 N nitric acid in a wide (at least 20-mm.) test tube until reaction is over. (*Caution:* The reaction starts suddenly.) Set aside. A solid should separate (Note 5).

D   REDUCTION

1. Metallic Sodium. To 4 or 5 ml. of acetone (or butanone) add 2 or 3 small pieces of metallic sodium. *Caution.* (Notes 6 and 7.)

E POLYMERIZATION

1. Paraformaldehyde. Hood. Evaporate over a hot water or steam bath 5 or 10 ml. of formalin (the commercial 40% solution of formaldehyde). Heat some of the residue in a test tube, and note the odor (*Hood*).

2. Paraldehyde. Add cautiously 1 drop of *cold* 80% sulfuric acid to 1 to 2 ml. of *pure* freshly distilled acetaldehyde, and mix well. Is there any evidence of chemical action? Add 3 to 5 ml. of cold water. Note the appearance of liquid. Explain.

3. Metaldehyde. Cool 5 ml. of pure anhydrous acetaldehyde in an ice–salt mixture, add a little anhydrous trichloroacetic acid, and allow to stand for about 2 hours at the low temperature. Note if a solid forms (Note 8).

F COLOR TESTS

1. Formaldehyde and Resorcinol. To 5 ml. of a dilute formaldehyde solution (Note 4) add 1 drop of 0.5% solution of resorcinol, and pour the resulting solution slowly and cautiously down the side of a well-inclined test tube (20 to 25 mm. diameter) containing about 5 ml. of concentrated sulfuric acid. Take care that the liquids do not mix and that the lighter liquid forms a distinct layer above the acid. A red zone, slightly violet in color, will appear, and above the red zone there will be a light flocculent precipitate.

2. Formaldehyde and Milk. Mix about 5 ml. of milk containing a trace of formaldehyde (about 0.1%) with an equal volume of concentrated sulfuric acid containing a small amount of ferric chloride (about one drop of $1 N$ solution) until all precipitate is dissolved. Repeat with a sample of milk free of formaldehyde (Note 9).

3. Schiff's Reagent (Note 10). To 5 ml. of Schiff's reagent add a few drops of the dilute formaldehyde solution. Let stand for about 5 minutes or until color develops. Repeat with the acetaldehyde solution and also with pure acetone and butanone.

To the colored solutions resulting from the aldehyde tests add *ca.* 10 ml. of $6 N$ sulfuric acid. If neither solution loses color, add more acid (Note 11).

G IDENTIFICATION

1. Dinitrophenylhydrazone. Dissolve 0.1 g. of powdered 2,4-dinitrophenylhydrazine (Note 12) in 1 to 2 ml. of *glacial* acetic acid in a centrifuge tube by gentle boiling. After it has dissolved, remove the flame, and, while still hot, add 2 to 4 drops of acetone (or other low-molecular-weight ketone or aldehyde) or *ca.* 0.1 g. if solid (Note 13). Keep hot

for 1 or 2 minutes. Let cool to room temperature. If no solid separates on scratching, add water, drop by drop, to the cold solution, but not more than the original volume of acetic acid (Note 14), until some solid separates. Then heat until the precipitate dissolves, and set aside to cool and crystallize (Note 15). Centrifuge, and wash once with acetic acid and twice with alcohol, centrifuging down each time. Crystallize from hot 96% ethyl alcohol, and take the melting point (Notes 16 and 17).

Repeat with an unknown aldehyde or ketone obtained from the instructor. Report the observed melting point.

Notes

1. This is made by shaking sodium bisulfite or sodium metabisulfite at room temperature with an amount of water insufficient to dissolve the solid (less than three times its weight) or by passing sulfur dioxide into a mixture of one part of sodium bicarbonate and three parts of water until the sodium bicarbonate dissolves.

2. Fehling's Solution I is made by dissolving 67.3 g. of $CuSO_4 \cdot 5H_2O$ in 1 liter of solution and Solution II, 100 g. of sodium hydroxide and 346 g. of Rochelle salt (sodium potassium tartrate), in 1 liter of solution.

3. Tollen's reagent is made by adding 1 drop of aqueous sodium hydroxide to about 20 ml. of dilute (0.05 N) silver nitrate, and dissolving the precipitate by the addition of dilute (about 0.05 N) ammonium hydroxide, drop by drop. *Caution:* As soon as the tests are finished, at once pour the solution down the drain, for an explosion may occur if it stands around. Do not make more than the specified amount.

4. Prepare a dilute solution of formaldehyde by one of the following methods.

(a) *Catalytic oxidation of methyl alcohol.* Pour 5 ml. of methyl alcohol into a 250-ml. Soxhlet extraction flask. Wrap a platinum wire around a glass rod of small diameter, so that a spiral about 2 cm. long is formed in the middle section of the wire, with one straight end 1 or 2 cm. long. Fasten the other end of this wire around a short piece of glass rod. The length of this straight wire and spiral should be so adjusted that the tip end of the wire is just above the surface of the alcohol when it is lowered into the flask and the rod rests on the top of the flask. Fold a piece of thin asbestos paper so that it forms a roof large enough to cover the mouth of the flask when it is placed loosely on it, thus admitting a limited supply of air.

Heat the platinum wire in a flame, lower it quickly into the flask, and cover it immediately with the asbestos roof. The platinum spiral should glow from the heat of the oxidation reaction taking place on the surface of the wire. The odor of formaldehyde will become apparent soon. If the air supply is properly regulated by adjusting the asbestos roof, the platinum wire will continue to glow for some time. Dilute with 10 ml. of water, and use for the tests described.

(b) *Oxidation of methanol by means of hot copper oxide.* Dissolve 2 ml. of methyl alcohol in 10 ml. of water. Wind a piece of stout copper wire around a lead pencil so that a closely coiled spiral about 2 cm. in length is formed, and leave about 20 cm. of the wire to serve as a handle. Heat the spiral in the oxidizing part of a flame, and plunge it while red hot into the solution of methyl alcohol. Withdraw the spiral, cool the liquid, and repeat the operation. Continue until the liquid has a decided odor of formaldehyde.

5. Nitric acid and potassium permanganate oxidatively cleave ketones between the C=O and a CH_2 group. In this case the product is a slightly soluble dibasic acid.

6. Completely decompose any unreacted sodium by first adding alcohol, before pouring into water.

7. The reaction is a complicated one, owing to the reducing action of sodium. The mixture contains the sodium salts of acetone, sec-propyl alcohol, and pinacol.

8. Paraldehyde is formed also. This may be sufficient to dissolve the solid.

9. This test is characteristic of formaldehyde and is not given by other aldehydes. An intense purple or violet color develops.

10. Schiff's reagent (fuchsine–sulfite reagent) is prepared by dissolving 0.5 g. of the pure red dye, p-rosaniline hydrochloride (fuchsine), in 0.5 liter of distilled water, filtering, and adding 0.5 liter of distilled water, saturated with sulfur dioxide. The solution should be almost colorless. It should be kept cool and dark.

11. This difference in stability of the color with Schiff's reagent differentiates formaldehyde from other aldehydes. It forms the basis of a qualitative method of testing for methanol in the presence of a large amount of ethyl alcohol.

12. This reagent, $H_2NNHC_6H_3(NO_2)_2$-2,4, melts at 198° with decomposition. It is not very soluble in cold glacial acetic acid. Its value here is due to the fact that all the derivatives it forms with aldehydes and ketones are solids. The melting points are so high that there usually is no trouble in crystallizing them.

13. For compounds of molecular weight near 300, use about twice as much. Although there should be an excess of the ketone, this should not be large when the ketone is insoluble in water. Often an immediate color change is observed when an aldehyde or ketone is added. The reaction usually takes place rapidly in glacial acetic acid, probably because acid catalysis is necessary. In case the reaction proves to be slow, repeat, but add 1 drop of concentrated hydrochloric acid first.

14. The reagent may separate if more water is added, especially if not enough ketone has been taken.

15. Many dinitrophenylhydrazones form supersaturated solutions and separate slowly, even when in contact with the solid. When crystallized from glacial acetic acid, the products are purer than when crystallized from a mixture of acetic acid and water.

16. For hydrazones very insoluble in alcohol, nitrobenzene is satisfactory for crystallization purposes. Naturally, this solvent, being high boiling, must be removed by washing with a volatile solvent (alcohol).

17. The melting points of a few 2,4-dinitrophenylhydrazones are: formaldehyde, 166°; acetaldehyde, 168°; propionaldehyde, 154°; acetone, 126°; butanone, 110–111°; cyclopentanone, 146–147°.

Questions

1. What can you say about the solubility of the bisulfite addition compound in pure water? in a solution having a high concentration of unreacted bisulfite?

2. How many isomers of hexamethylenetetramine are possible when: (a) one hydrogen atom is replaced by deuterium; (b) two hydrogen atoms are replaced by deuterium?

3. Is aldol present while any of the tests are being made?

4. What statement can you make relative to the difference in ease of oxidation of aldehydes and ketones?

5. Which are the stronger reducing agents: aldehydes or ketones?

6. Why does permanganate oxidize ketones better in alkaline than in neutral solution?

7. What solid is obtained from cyclohexanone in C?

8. What types of compounds give the iodoform test?

9. What other metals convert acetone to pinacol?

10. Explain how you have been able to reverse a chemical reaction.

11. Write the structures of aldol, paraldehyde, paraformaldehyde, and metaldehyde.

12. In what respects does formaldehyde resemble acetaldehyde chemically?

13. In what respects does it differ chemically?

14. What are the oxidation and reduction products of formaldehyde?

15. How do aldehydes and ketones resemble each other chemically?

16. How do aldehydes and ketones differ from each other chemically?

17. Write equations for reactions in A, B, C, D, E, and G.

18. Why is a fairly high-melting point a desirable property in a derivative?

19. Calculate the equilibrium composition of the mixtures obtained by heating the following mixtures to 300° in a sealed 1-liter vessel containing some zinc–copper alloy:

(a) 0.1 mole ethyl alcohol and 0.1 mole acetone.

(b) 0.2 mole ethyl alcohol and 0.2 mole acetone.

(c) 0.1 mole ethyl alcohol and 0.1 mole isopropyl alcohol.

(d) 0.2 mole ethyl alcohol and 0.2 mole isopropyl alcohol.

(e) 0.2 mole acetaldehyde and 0.2 mole isopropyl alcohol.

(f) 0.1 mole acetaldehyde and 0.1 mole acetone.

Assume that the equilibrium is not altered by temperature change. Explain the effect of changing concentrations.

Chapter 26

AMINES

A primary aliphatic amine RNH_2 may be obtained by: (a) the action of ammonia or of a suitable ammonia derivative, for example sodamide or phthalimide, on an alkyl halide or other alkylating agent, (b) the action of ammonia on an alcohol, (c) catalytic hydrogenation of a nitrile, oxime, or nitro compound; (d) the reduction of a nitrile, oxime, or nitro compound; (e) the Hofmann degradation of the amide of an acid.

(a)
$$NH_3 + C_2H_5I \longrightarrow C_2H_5NH_3I$$

$$C_2H_5NH_3I + KOH \longrightarrow C_2H_5NH_2 + KI + H_2O$$

$$NaNH_2 + C_2H_5I \longrightarrow C_2H_5NH_2 + NaI$$

$$C_6H_4(CO)_2NH + KOH \longrightarrow C_6H_4(CO)_2NK + H_2O$$

$$C_6H_4(CO)_2NK + IC_2H_5 \longrightarrow C_6H_4(CO)_2NC_2H_5 + KI$$

$$C_6H_4(CO)_2NC_2H_5 + HCl + 2H_2O \longrightarrow$$
$$C_6H_4(CO_2H)_2 + C_2H_5NH_3Cl$$

$$C_2H_5NH_3Cl + KOH \longrightarrow C_2H_5NH_2 + KCl + H_2O$$

(b)
$$C_2H_5OH + NH_4Cl \xrightarrow{350°} C_2H_5NH_3Cl + H_2O$$

$$C_2H_5OH + NH_3 \xrightarrow[ZnCl_2]{300°} C_2H_5NH_2 + H_2O$$

(c)
$$C_2H_5C\equiv N + 2H_2 \longrightarrow C_2H_5CH_2NH_2$$

$$C_2H_5NO_2 + 3H_2 \longrightarrow C_2H_5NH_2 + 2H_2O$$

$$C_2H_5CH\!=\!NOH + 2H_2 \longrightarrow C_2H_5CH_2NH_2 + H_2O$$

(d)
$$C_2H_5C\equiv N + 4Na + 4C_2H_5OH \longrightarrow$$
$$C_2H_5CH_2NH_2 + 4C_2H_5ONa$$

(e)
$$CH_3CONH_2 + Br_2 + NaOH \longrightarrow$$
$$CH_3CONHBr + NaBr + H_2O$$

$$CH_3CONHBr + NaOH \longrightarrow CH_3N\!=\!C\!=\!O + NaBr + H_2O$$

$$CH_3N\!=\!C\!=\!O + 2NaOH \longrightarrow CH_3NH_2 + Na_2CO_3$$

26.11 Alkylation of Ammonia. In method a reaction usually is carried out between the alkyl halide and ammonia in alcoholic solution by heating for a few hours at 100° in sealed tubes or in an autoclave. Sometimes the reaction mixture is allowed to stand for a long time at room temperature. Unsaturation often is observed and may be so extensive in the case of tertiary halides that little or no amine is formed. Even with secondary halides, the tendency to form the olefin rather than the amine may be so great that the yields are quite low, as shown by the formation of a mixture of propylene and sec-propyl amine from sec-propyl iodide and ammonia at 100°, and of 2-bromo-2-butene from 2,3-dibromobutane and ammonia at 110°, with little of the desired 2,3-diaminobutane.

The yield of the primary amine RNH_2 in the reaction of an alkyl halide RX with ammonia is diminished also by subsequent reactions, as follows:

$$RNH_3X + NH_3 \rightleftharpoons RNH_2 + NH_4X$$

$$RNH_2 + XR \rightarrow R_2NH_2X$$

$$R_2NH_2X + NH_3 \rightleftharpoons R_2NH + NH_4X$$

$$R_2NH + XR \rightarrow R_3NHX$$

$$R_3NHX + NH_3 \rightleftharpoons R_3N + NH_4X$$
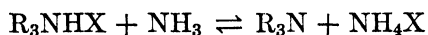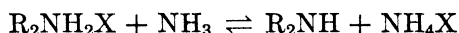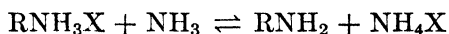
The reversible reactions are essentially ionic and therefore rapid, for they involve proton transfer from one base to another. The primary amine RNH_2 and the secondary amine R_2NH react with more alkyl halide RX in the same way ammonia does. The result is a mixture of the amines and their salts. Since the rates of formation of the primary amine RNH_2 and of the secondary amine R_2NH are dependent in part on the respective concentrations of ammonia and of the primary amine, it is evident that the ratio of the concentrations of these two should at all times strongly favor the former, when the primary amine is the desired product.

One modification of method a is the use of sodamide in place of ammonia. It has the advantage, compared to ammonia, that it reacts more rapidly and gives a purer product, owing to the fact that less of the secondary and tertiary amines are formed. It has the disadvantage that unsaturation is more likely to take place.

Another modification of method a is Gabriel's synthesis, in which potassium phthalimide replaces ammonia. This compound reacts, when heated, with primary and secondary alkyl halides and with many other types of halogen compounds. The product, an N-substituted

phthalimide, on hydrolysis yields a primary amine (or salt, if an acid
is present). This method has the advantage that the primary amine
so obtained is free of any secondary or tertiary amine. Sometimes the
potassium salt of benzamide is used in place of potassium phthalimide.
Here also the final product is free of any secondary or tertiary amine.

**26.12 Direct Replacement of the Alcoholic Hydroxyl Group by
the Amino Group.** In method *b* usually the mixture of the alcohol
and the ammonium salt must be heated for some time in a sealed tube
or autoclave at a fairly high temperature (300–350°). Secondary and
tertiary amines are by-products. Alcohols sometimes react directly
with ammonia when a gas-phase mixture of the two is passed at elevated
temperature over a specially prepared dehydrating catalyst (Al_2O_3, TiO_2,
etc.), with elimination of water. This method is complicated by unsatu-
ration and by the formation of secondary and tertiary amines. For
the gas-phase reaction, ΔH from bond energies is -5 kcal.

**26.13 Hydrogenation of Nitriles, Oximes, and Nitro Com-
pounds.** In method *c* reaction can be carried out in the presence of
hydrogenation catalysts, such as platinum and Raney nickel. Nitriles
are the least reactive, and nitro compounds are the most reactive.
Nitriles and oximes are prone to form secondary amines and hydro-
carbons, especially if any moisture is present. The secondary reaction
may be controlled if acetic anhydride is the solvent, since then the
primary amine is acetylated as it is formed. The reduction of oximes
offers a means of converting aldehydes to amines of the same number
of carbon atoms, since aldehydes are easily converted to oximes:

$$C_2H_5CHO + H_2NOH \rightarrow C_2H_5CH{=}NOH$$

For the gas-phase hydrogenations of nitriles, oximes, and nitro com-
pounds the ΔH values calculated from bond energies are approximately
-34, -78, and -200 kcal., respectively. Naturally, care must be
taken that the reaction does not proceed explosively, especially in the
case of the nitro compounds, where $-\Delta H$ is so large.

26.14 Reductions, method *d*, are accomplished by different re-
agents. Thus nitriles give best results with sodium and alcohol. It is
important that the reactants be anhydrous; otherwise, hydrolysis of
the nitrile diminishes the yield of amine. Reduction of oximes may be
accomplished by means of sodium amalgam in acetic acid. Nitro com-
pounds can be reduced by a number of reducing agents, among them
sodium and alcohol, tin and hydrochloric acid, zinc and acetic acid (see
Chapter 33).

26.15 The Hofmann Degradation. Method *e* often is used to
prepare a primary aliphatic amine from the next higher amide. It is

an important method because amides can be obtained easily from the respective acids. The formation of the N-bromoamide takes place rapidly at room temperature. For the formation of the isocyanate and its subsequent hydrolysis to the amine, heating in a strongly basic solution is necessary.

In Experiment 26–1, methylamine is prepared from acetamide. The reactions are quite exothermic. On this account proper control must be exercised. The procedure followed in Experiment 26–1 is satisfactory for almost any scale, since the rate of addition of one reactant acts as the control.

A modification of the Hofmann degradation is the use of the azide, instead of the N-bromoamide (Curtius degradation). An acid is degraded through the steps ester, hydrazide, azide, urethane, amine.

$$RCOOH + HOC_2H_5 \longrightarrow RCOOC_2H_5 + H_2O$$

$$RCOOC_2H_5 + H_2NNH_2 \longrightarrow RCONHNH_2 + C_2H_5OH$$

$$RCONHNH_2 + HONO \longrightarrow RCON_3 + 2H_2O$$

$$RCON_3 + HOC_2H_5 \xrightarrow{heat} RNHCOOC_2H_5 + N_2$$

$$RNHCOOC_2H_5 + 2NaOH \longrightarrow RNH_2 + C_2H_5OH + Na_2CO_3$$
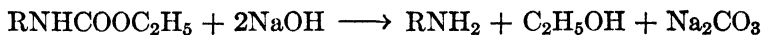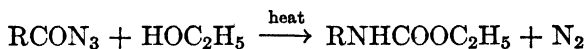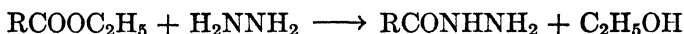
The azide can be prepared, but usually less satisfactorily, by the action of the acid chloride on sodium azide. The acid azide when heated alone decomposes to nitrogen and isocyanate, which can be hydrolyzed to the amine. Yields usually are less satisfactory.

$$RCON_3 \rightarrow RN{=}C{=}O + N_2$$

Usually yields in the Curtius degradation are better than in the Hofmann degradation. On this account the Curtius degradation is much used in synthetic work.

SIDE REACTIONS in the Hofmann degradation which may diminish the yield are: (1) hydrolysis of the amide or of the bromoamide, (2) formation of the nitrile of the acid, instead of rearrangement, (3) formation of a disubstituted urea from the reaction of the cyanate with the desired primary amine:

$$CH_3CONH_2 + NaOH \rightarrow CH_3COONa + NH_3$$

$$CH_3CONHBr + NaOH \rightarrow CH_3CN + NaOBr + H_2O$$

$$CH_3{-}N{=}C{=}O + NH_2CH_3 \rightarrow CH_3NH{-}CO{-}NHCH_3$$
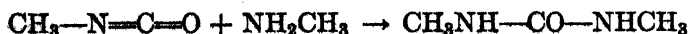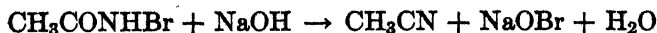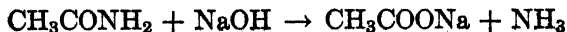
Hydrolysis of the amide is possible because, although it is largely converted to the bromoamide, there is an equilibrium among amide, hypobromite, and bromoamide. This reaction may explain the presence of ammonia in the final product. Sometimes, as in the case of higher amides, the nitrile reaction becomes quite important. Then hydrolysis of the nitrile leads to the formation of ammonia and the acid corresponding to the original amide. The formation of the disubstituted urea need not result in any loss since it undergoes hydrolysis under the conditions of the experiment. However, if the alkyl groups are large, the slight solubility of the compound in water may hinder the hydrolysis:

$$CH_3NH{-}CO{-}NHCH_3 + 2NaOH \rightarrow 2CH_3NH_2 + Na_2CO_3 + H_2O$$

Sometimes the second step is carried out in an alcoholic solution with sodium ethoxide. Under these conditions the product is an urethane, $RNHCOOR'$, formed by the reaction of the isocyanate with alcohol, as shown in the following reactions in the case of propionbromamide.

$$C_2H_5CONHBr + NaOC_2H_5 \rightarrow C_2H_5N{=}C{=}O + NaBr + C_2H_5OH$$

$$C_2H_5N{=}C{=}O + HOC_2H_5 \rightarrow C_2H_5NHCOOC_2H_5$$

If the urethane is purified (many are solid and can be purified by crystallization), the amine can be obtained in a very pure state by alkaline hydrolysis of the urethane:

$$C_2H_5NHCOOC_2H_5 + 2NaOH \rightarrow C_2H_5NH_2 + C_2H_5OH + Na_2CO_3$$
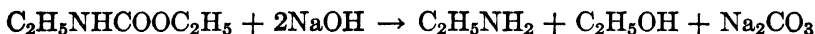
Experiment 26–1   Preparation of Methylammonium Chloride (Methylamine Hydrochloride)

HOFMANN DEGRADATION OF ACETAMIDE. Equip a 1-liter three-necked flask (Note 1) with a separatory funnel (or a wide-bore dropping funnel), a thermometer with bulb near the top of the flask, and a wide bent exit tube leading to a condenser (medium or long). In the flask dissolve 1.6 to 1.7 moles of sodium hydroxide (Note 2) in ca. 150 ml. of water. To the lower end of the condenser attach a suitable device for absorbing the volatile amine in hydrochloric acid without allowing the acid to be drawn back into the reaction flask when the pressure drops (Note 3). Use enough dilute (ca. 20%) aqueous hydrochloric acid to furnish 0.7 to 0.8 moles of hydrogen chloride.

At the hood place 0.50 mole of acetamide and 0.5 mole of bromine (*Caution:* Note 4) in a 500-ml. flask. Cool in ice water, and add a cooled solution of ca. 0.8 mole of sodium hydroxide (Note 2) in 400 ml. of water with cooling and shaking, keeping the temperature below 20° to prevent

decomposition of sodium hypobromite.   Perform the next operation without much delay (Note 5).

Using a few pieces of hard baked porous tile to prevent bumping (Note 6), heat the sodium hydroxide solution to boiling in the 1-liter flask.   Transfer a part of the N-bromoacetamide to the dropping funnel, and allow this to flow into the boiling sodium hydroxide solution. Sometimes the heat of the reaction will keep the solution boiling.   Apply heat as soon as necessary to keep the liquid boiling, in order to boil out the methylamine as it is formed (Note 7).   After all the solution has been added, continue the heating, and distil off methylamine and water so long as the distillate at the condenser's end contains much methylamine (Note 8).

Evaporate the solution in a porcelain dish (*Hood*) to a small volume over a free flame.   Complete the evaporation until hydrogen chloride is no longer evolved, either by heating over a small free flame while keeping the dish in constant motion to avoid spattering and loss of product by volatilization, or by heating over a steam or hot-water bath. The latter is much the slower procedure.   Finally dry the residue carefully but completely in an oven at 100° for about ½ hour (Note 9). Weigh the crude product (Note 10).

EXTRACTION OF METHYLAMMONIUM CHLORIDE FROM AMMONIUM CHLORIDE.   Place the solid and 100 ml. of absolute alcohol in a 200-ml. conical flask, and heat under a reflux condenser and by means of a hot-water bath for several minutes.   Decant the hot liquid through a small fluted filter paper, *taking care that it does not evaporate and become cool while on the filter.*   Cool the filtrate to about 0°.   Collect the solid by suction filtration on a small funnel (refer to Section 5.4), avoiding needless evaporation.   Use the filtrate for a second hot extraction of the crude methylammonium chloride.   Repeat the extraction process as long as a worth-while crop of crystals is obtained.   Evaporation of the final filtrate to about one fourth of its volume and cooling will yield an additional small amount of methylammonium chloride.   Calculate the percentage yield (Note 11).

Notes

1. Or use a distilling flask, and attach the thermometer and dropping funnel by means of a 2-hole stopper.

2. Flake sodium hydroxide technical grade is satisfactory.   *Caution:* Spilled caustic solution, which rapidly attacks wool, skin, and wood, should at once be neutralized with acid and wiped up.

3. There should be a wide area of contact between the gas and the acid.   An inverted funnel barely dipping under the surface of the liquid is satisfactory.   Methylamine will escape from the apparatus if there is a leak, and the amount escaping will be greater, the greater the back pressure.

4. *Caution:* Don't breathe bromine vapor. In case bromine comes in contact with the skin, wash the skin immediately with alcohol or much water and then with aqueous sodium bicarbonate.

5. In case the precipitation of N-bromoacetamide at this stage is too heavy, add a small amount of water (50 or 100 ml.), and warm to room temperature. On long standing the compound decomposes.

6. Soft baked porous tile rapidly disintegrates in the hot caustic solution.

7. The slight loss of smoke of methylammonium chloride is insignificant.

8. The distillate will be basic to litmus even when the concentration of the amine is insignificantly small. When 1 ml. of the distillate contains less than 0.001 equivalent of base (by titration with acid, methyl red being used as indicator), the recovery of the remaining amine is not practical. Usually it is not necessary to make a test until about 200 ml. of liquid has distilled or until the temperature registered by the thermometer ceases to rise. It may take 1.5 to 2 hours to carry out this step.

9. The dish must *not* be put in the oven until all hydrochloric acid is driven off. Care must be taken not to place the dish close to the heating element if an electrically heated oven is used. Methylammonium chloride sublimes easily. The dish should be examined at intervals to see that the product does not sublime.

10. This is not pure methylammonium chloride, for it is contaminated by ammonium chloride. The removal of the latter depends on the greater solubility of the former in absolute alcohol.

11. The yield is 60%.

Questions

1. What reaction takes place between bromine and sodium hydroxide, in aqueous solution, in the cold?

2. What reaction takes place between bromine and sodium hydroxide, in aqueous solution, when heated?

3. What happens when hydrobromic acid is added to N-bromoacetamide?

4. Methylamine can be called methylammonia or aminomethane. Chemically, is it like ammonia or like methane? Explain.

5. How does ammonium chloride happen to be a contaminant? Explain by writing the equations for the reactions.

6. Outline a procedure for removing ammonium chloride.

7. What reaction takes place if the methylamine is not removed as it is formed?

8. Why does smoke form?

9. How can the loss of smoke be avoided?

10. By what other methods may methylamine be prepared?

11. Which of these are general methods?

12. Show by equations how methyl alcohol may be prepared from acetic acid.

13. What is meant by the word *degradation*, as used in organic chemistry?

14. What are the probable impurities in the crude and final products?

15. What steps have been taken to remove them?

Experiment 26–2 Properties of Amines

A LIBERATION FROM HYDROCHLORIDE. In a test tube place a small amount of methylammonium chloride (0.5 to 1.0 g.), and a few milliliters of a concentrated aqueous solution of sodium hydroxide (or 1 to

2 g. of solid sodium hydroxide and 1 to 2 ml. of water). Close the vessel with a stopper carrying a short piece of glass tubing. Heat gently. Note the odor of the gas evolved. Try to ignite the gas at the end of the tube (Note 1).

B REACTION WITH SODIUM NITRITE AND HYDROCHLORIC ACID. In a test tube prepare an ice-cold solution of methylammonium chloride (about 0.01 mole) by adding ice, so that some remains. Add an equimolal amount of sodium nitrite and then, drop by drop, with agitation, an equivalent amount of hydrochloric acid. Run a blank at the same time, to note the appearance of the solution in the absence of methylammonium chloride (Note 2). Repeat with diethylammonium chloride (or di-*n*-propylammonium chloride), except that only a slight excess of acid need be added (Notes 3 and 4). Repeat with triethylammonium chloride (or tri-*n*-propylammonium chloride).

Notes

1. Only gentle heating is necessary to obtain a volatile base this way.

2. It is necessary to observe the behavior of the blank, in order to allow for decomposition of nitrous acid to nitrous anhydride. An excess of sodium nitrite should be avoided.

3. In case the amine is available and the salt is not, add c.p. hydrochloric acid, drop by drop, to some of the base, until just acid to litmus.

4. Lower secondary amines yield yellowish solutions; higher yield oils.

Questions

1. Write the equations for the reactions in A and B.

2. How do you account for the fact that, when ammonia is oxidized to nitric oxide by oxygen or when nitric oxide is reduced to ammonia by hydrogen, heat is liberated?

3. Which is the stronger base: ammonia or methylamine?

Chapter 27

AMIDES

Amides may be obtained by: (*a*) the ammonolysis of acid chlorides, (*b*) the ammonolysis of acid anhydrides, (*c*) the ammonolysis of esters, (*d*) the ammonolysis of organic acids, (*e*) the hydration of nitriles. Urea, the amide of carbonic acid, is obtained also by (*f*) the rearrangement of ammonium cyanate.

(*a*) $\qquad CH_3COCl + 2NH_3 \longrightarrow CH_3CONH_2 + NH_4Cl$

$\qquad\qquad COCl_2 + 4NH_3 \longrightarrow NH_2CONH_2 + 2NH_4Cl$

(*b*) $\qquad (CH_3CO)_2O + NH_3 \longrightarrow CH_3CONH_2 + CH_3COOH$

$$\begin{array}{c} CH_2CO \\ | \qquad\quad \Large\rangle O + NH_3 \longrightarrow \\ CH_2CO \end{array} \quad \begin{array}{c} CH_2CONH_2 \\ | \\ CH_2COOH \end{array}$$

(*c*) $\qquad CH_3COOC_2H_5 + NH_3 \longrightarrow CH_3CONH_2 + C_2H_5OH$

$$\begin{array}{c} CH_2COOC_2H_5 \\ | \qquad\qquad + 2NH_3 \longrightarrow \\ CH_2COOC_2H_5 \end{array} \quad \begin{array}{c} CH_2CONH_2 \\ | \qquad\qquad + 2C_2H_5OH \\ CH_2CONH_2 \end{array}$$

(*d*) $\qquad CH_3COOH + NH_3 \rightleftharpoons CH_3COONH_4$

$$CH_3COONH_4 \overset{\text{heat}}{\rightleftharpoons} CH_3CONH_2 + H_2O$$

(*e*) $\qquad 2CH_3CN + 2H_2O_2 \xrightarrow{\text{KOH}} 2CH_3CONH_2 + O_2$

(*f*) $\quad (\overset{+}{N}H_4)_2SO_4^= + 2\overset{+}{K}[NCO]^- \rightleftharpoons 2\overset{+}{N}H_4[NCO]^- + \overset{+}{K}_2SO_4^=$

$$\overset{+}{N}H_4[NCO]^- \longrightarrow NH_2CONH_2$$

$$CH_3\overset{+}{N}H_3\bar{C}l + K[NCO]^- \rightleftharpoons CH_3\overset{+}{N}H_3[NCO]^- + \overset{+}{K}\bar{C}l$$

$$CH_3\overset{+}{N}H_3[NCO]^- \longrightarrow CH_3NHCONH_2$$

$$(CH_3)_2\overset{+}{N}H_2\bar{C}l + \overset{+}{K}[NCO]^- \rightleftharpoons (CH_3)_2\overset{+}{N}H_2[NCO]^- + \overset{+}{K}\bar{C}l$$

$$(CH_3)_2\overset{+}{N}H_2[NCO]^- \longrightarrow (CH_3)_2NCONH_2$$

The amides of dibasic acids, except for those that form cyclic imides, are obtained analogously. In order to obtain the diamides of acids that

readily form cyclic imides, namely, succinic and glutaric acid and derivatives, the operations must be carried out under mild conditions; otherwise, ring closure may take place.

Imides may be obtained by heating the amide with the acid chloride or the acid anhydride similar to a and b above. The cyclic imides of succinic and glutaric acids result when their ammonium salts are heated (method d), or when their monoamides or diamides are heated (method g). Hence, any method of producing amides which involves heating leads, in the case of these acids, to the cyclic imide.

(a) $CH_3COCl + CH_3CONH_2 \xrightarrow{\text{heat}} (CH_3CO)_2NH + HCl$

(b) $(CH_3CO)_2O + CH_3CONH_2 \xrightarrow{\text{heat}} (CH_3CO)_2NH + CH_3COOH$

(d) $\begin{array}{l} CH_2COONH_4 \\ | \\ CH_2COONH_4 \end{array} \xrightarrow{\text{heat}} \begin{array}{l} CH_2CO \\ | \quad\quad\ \ \rangle NH + NH_3 + 2H_2O \\ CH_2CO \end{array}$

(g) $\begin{array}{l} CH_2CONH_2 \\ | \\ CH_2COOH \end{array} \xrightarrow{\text{heat}} \begin{array}{l} CH_2CO \\ | \quad\quad\ \ \rangle NH + H_2O \\ CH_2CO \end{array}$

 $\begin{array}{l} CH_2CONH_2 \\ | \\ CH_2CONH_2 \end{array} \xrightarrow{\text{heat}} \begin{array}{l} CH_2CO \\ | \quad\quad\ \ \rangle NH + NH_3 \\ CH_2CO \end{array}$
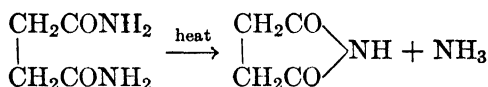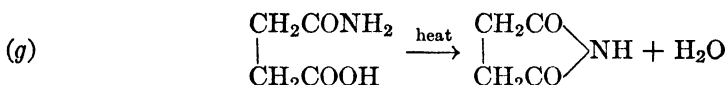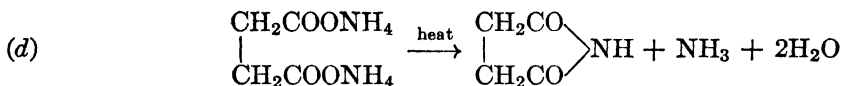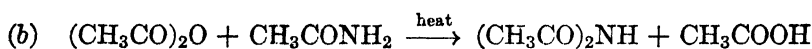
In all the reactions in which ammonia enters, the substitution of a primary or secondary amine for the ammonia leads to the formation of an amide in which one or both hydrogen atoms of the amido group are replaced by an alkyl radical.

27.11 Ammonolysis of Acyl Chlorides and Anhydrides. In methods a and b reaction may be carried out with aqueous or gaseous ammonia. The acid chlorides, especially the lower ones, sometimes react violently, owing to the rapid rate and strongly exothermic nature of the reaction. Anhydrides often react rapidly, with considerable heat evolution. Reactants of higher molecular weight, even acid chlorides, may require heating. Reaction is faster and more complete under basic conditions (refer to 21.13). From the preparative point of view, method a is preferable if one wishes a good yield on the basis of the acid, and method b if on the basis of the ammonia (or amine). These reactions are useful in the identification of acids and amines by conversion to solid amides or substituted amides ($RCONH_2$, $RCONHR'$ or $RCONR'_2$) with the appropriate reactant.

27.12 Ammonolysis of Esters. In method c reaction generally proceeds rather slowly (hours or days at room temperature) but may take place rapidly with a reactive ester like ethyl oxalate. Even

methyl butyrate reacts satisfactorily in a half day under agitation. Increase in molecular weight and, more particularly, branching of the carbon chain of the acid at the *alpha* position decrease the rate of reaction. Thus methyl malonate is readily converted into a diamide by aqueous ammonia at room temperature, but methyl diethylmalonate $(C_2H_5)_2C(COOCH_3)_2$, is not affected after 30 hours.

For the gas-phase reaction between ethyl acetate and ammonia, ΔH is -2.1 kcal. when calculated from bond energies and resonance energies. The gas-phase reaction, therefore, appears to be slightly exothermic. Calculation for the reaction in aqueous solution, if heats of vaporization are taken into account and heats of dilution neglected, gives a value of approximately -10 kcal. Calculation with heats of formation gives a similar value.

The comparatively low yield probably is due in part to incompleteness of reaction and in part to hydrolytic reactions, although it should be noted that acetamide is little altered in the presence of cold water. The product is recovered by distillation, rather than by evaporation of the solution, because acetamide is too soluble in water to be obtained pure in this way (Experiment 27–1).

The reaction of ethyl malonate with urea to form barbituric acid (Experiment 27–2) is similar to ammonolysis of an ester, for urea resembles ammonia, and the product, the ureide of malonic acid, is essentially a cyclic diimide. The rate is much lower than the ammonolysis of ethyl acetate and is increased by basic catalysis, sodium butoxide. Butyl alcohol is the solvent, to obtain a sufficiently high reaction temperature. Water must be excluded, to avoid hydrolysis of the ester and of urea. The reactions are shown below.

$$2C_4H_9OH + 2Na \rightarrow 2C_4H_9ONa + H_2$$
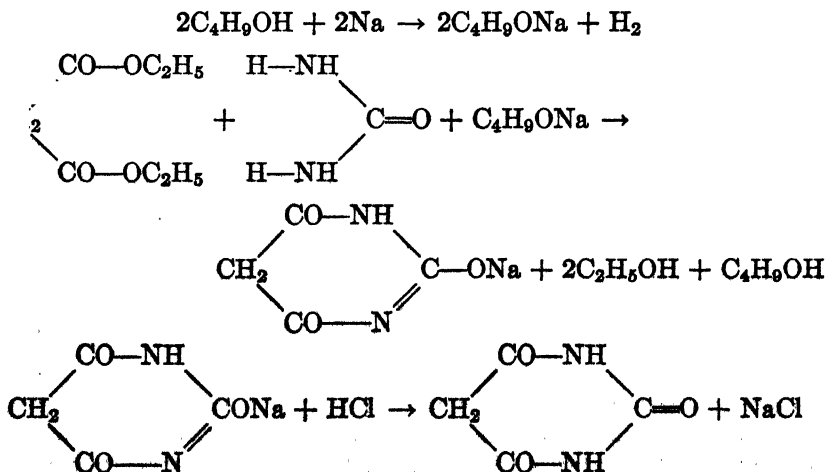
These reactions may be extended to the preparation of substituted barbituric acids, starting with substituted malonic esters instead of malonic ester.

27.13 Ammonolysis of Acids. In method d reaction may be carried out by heating the dry ammonium salt in a sealed tube or by heating a solution of the ammonium salt in the carboxylic acid; for example, acetamide is prepared by heating ammonium acetate in glacial acetic acid. The latter procedure has the advantage that the reaction may be driven to completion by removing one of the products, namely, water, by distillation, as it is formed. Also the reaction is more rapid since it is acid-catalyzed, for it actually takes place between the undissociated acid and ammonium ion.

When ammonium acetate is converted to acetamide, the reaction in 1 hour proceeds less than one tenth of the way to equilibrium at 125°, whereas at 212° it goes 98.5% to equilibrium. The respective equilibrium values at 125° and 212° are 75.1% and 84.0% conversion to acetamide. This would indicate that heat is absorbed when acetamide and water are formed from ammonium acetate. From these data ΔH is $+2.5$ kcal., by the use of the van't Hoff equation (Equation 1–17). When calculation is made from bond energies and resonance energies (Tables 1–1 and 1–2), ΔH is $+1.9$ kcal. The agreement here is quite good. In dilute aqueous solution at 172°, equilibrium is reached in 5 days. Under these conditions ΔH is $+5.3$ kcal.

The rate of amide formation from the dry ammonium salt is less for the higher compounds and even less if the chain is branched, especially at the *alpha* position.

27.14 Hydration of Nitriles. In method e the reaction is carried out best with aqueous–alcoholic hydrogen peroxide under basic conditions. Hydration often can be accomplished, but less satisfactorily, by heating under pressure with water at 180° or, in the case of unreactive amides, by dissolving the nitrile in cold concentrated sulfuric acid and then pouring into water.

$$CH_3C{\equiv}N + H_2O \rightarrow CH_3CONH_2$$

27.15 Rearrangement of Ammonium Cyanate. In method f the reaction takes place in solution but is quite slow at room temperature.

The reacting materials are a cyanate, usually the potassium salt, and an ammonium salt, preferably the sulfate, because sulfates in general have low solubilities in anhydrous alcohols, which may be used for extracting urea from the dry reaction mixture. Isobutyl alcohol has an advantage over absolute ethyl alcohol in that urea is much less

soluble in the former at room temperature and yet is fairly soluble at the boiling temperature.

27.16 Side Reactions. In the reaction of an acid chloride with ammonia or with a substituted ammonia only half the base is converted to the amide, owing to the formation of ammonium chloride or similar compounds. For this reason the anhydride is preferred, when an amine is to be acylated. Sometimes a suitable basic substance is added, for example aqueous sodium carbonate or sodium hydroxide, if the acid chloride does not react rapidly with it, as is the case with benzoyl chloride. Diacylated amines (imides) can be formed by heating with an excess of the acid chloride or anhydride.

In the ammonolysis of esters, some hydrolysis of the ester may occur when water is present. Usually, however, side reactions are not important. This is true also of ammonolysis of acids. In the barbituric acid reaction (Experiment 27–2) urea may decompose to biuret if it remains undissolved during heating.

$$NH_2CONH_2 + NH_2CONH_2 \rightarrow NH_2CONHCONH_2 + NH_3$$
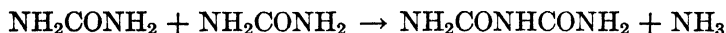
Hydration of nitriles is accompanied by hydrolysis of the resulting amides. Under acidic or basic conditions the amides react more rapidly than do the nitriles.

Rearrangement of cyanates, when carried out in the presence of water, is accompanied by hydrolysis of cyanate ion and of the desired product. This is promoted by the necessity of evaporating the water, as in Experiment 27–3, The Preparation of Urea. The solution should be essentially neutral since the hydrolysis is both acid-catalyzed and base-catalyzed.

Experiment 27–1   Preparation of Acetamide

In an 0.5- or 1-liter conical flask place 1 mole of ethyl acetate and sufficient concentrated ammonium hydroxide (sp. gr. 0.90, Note 1) to furnish 1.5 to 2.5 moles of ammonia (Note 2). Stopper the flask, and set aside until all the ethyl acetate has reacted. The flask should be shaken frequently during this period. Place the liquid in a 500-ml. round-bottomed flask, attach a *short* fractionating column, and distil *rapidly* through a long water-jacketed condenser (80- to 90-cm. jacket), taking care that ammonia, which is copiously evolved at first, does not escape into the laboratory (Note 3). When the distilling temperature reaches 125° to 130°, allow the acetamide to cool somewhat, and transfer it while still warm to a distilling flask of proper size, attached to an *air-cooled* condenser (Note 4).

Continue the distillation but more slowly, to facilitate fractionation. Collect fractions as follows, the last in a previously weighed small flask or sample bottle: (1) up to 195°; (2) 195–212°; (3) 212–216° (Note 5). If the material solidifies in the condenser tube, apply heat from a fishtail burner to melt it. Redistil fractions 1 and 2 *slowly* in a still smaller distilling flask, collecting the same fractions as before. Calculate percentage yield on the last fraction, and calculate also the corrected boiling point. Determine the melting point of this fraction, first pressing out 1 to 2 g. on a good absorbing medium, such as filter paper or porous tile, to remove any liquid film due to moisture absorbed at the surface.

Crystallize 0.5 to 0.7 g. by warming with a mixture of 3 ml. of benzene and 3 ml. of ethyl acetate in a test tube until dissolved and then cooling. Collect by suction filtration, using a small Hirsch funnel (Note 6). Determine the melting point of the recrystallized material, as before.

Notes

1. Determine the density unless it is known with certainty.

2. The yield of acetamide is dependent in part on the time of standing, the skill in recovery, and the molal ratio of ammonia to ester. When the ratio is 1.5 to 2, the yield is about 50% after 2 days' standing, and 70 to 75% after 5 to 7 days; when the ratio is 2.5, the yield is 60% after 2 days and 75% after 5 to 7 days. It is not profitable to increase the ratio much above 2 because of the greater inconvenience in handling larger amounts of ammonia. Standing longer than 5 days does not seem to improve the yield; it is probable that the yield drops slowly.

3. If a hood is not available, use as the receiver a distilling flask or a suction flask, and pass the exit gas from this flask through three 1-liter flat-bottomed flasks, the first two containing about 0.5 liter of water each, the last about 0.5 liter of dilute sulfuric acid. Rubber stoppers may be used in the absorbing train. Arrange the apparatus so that the contents of the flasks cannot suck back. Note that there will be an increase in the volume of the liquid, that the density of aqueous ammonia is below that of water, and that water becomes quite warm when ammonia dissolves rapidly in it. Take suitable action to overcome these disadvantages.

4. Refer to 7.21, Air Condensers.

5. The temperature ranges are approximate only because of the large stem corrections and variations in different thermometers. Start collecting the last fraction when the temperature is substantially constant, around 212° to 215°.

6. Refer to Section 5.4.

Questions

1. What is the evidence that reaction takes place?

2. How can one eliminate the possibility of the absorbing liquid being sucked back from the absorption train?

Notes

1. It is essential that apparatus and materials be anhydrous. The ethyl malonate should be freshly distilled under reduced pressure (94–96° at 20 mm.; Chapter 8) and the urea should be oven-dried just before use. Start with the oven temperature at *ca.* 90° and raise it to *ca.* 110°. In case the urea liquefies and later solidifies, as it often does when moist, grind it to a very fine powder, and reheat. Do not heat needlessly long, since urea changes to biuret fairly rapidly at the melting point. Check the purity by a melting-point determination, rapidly taken.

Start and complete the experiment on the same day, since the product discolors when wet. Prepare apparatus and materials ahead of time.

2. Refer to 15.17. If the stirrer is sealed with mercury, take care that mercury is not drawn into the reaction mixture. The stirrer can be dispensed with entirely if the flask and contents are shaken at very frequent intervals until the urea has dissolved. However, the yield usually is low by 5 or 10% under these conditions, probably because urea settles to the bottom and does not dissolve well. The stirrer can be dispensed with during the time the metallic sodium is reacting.

3. *Caution:* Refer to Experiment 15–1, Note 10, for handling metallic sodium. Some excess of sodium is desirable, for then the reaction proceeds more rapidly.

4. The reaction mixture should be free of sodium hydroxide (see Question 1); hence, the worker should trim off *all* the crust and then try to cut the desired amount of sodium all in one block so that the minimum of area is exposed to atmospheric moisture. The proper-sized blocks can be cut with the aid of calculations based on the density of sodium. The amount of sodium can be changed a little from that specified; however, it is well to remember that the more sodium taken the more sodium chloride impurity in the crude product.

5. This volume has been found to be satisfactory. The yield is much lower with 25 ml.

6. Water can be removed from 1-butanol conveniently and completely by distillation (12.12).

7. The solution of sodium butoxide in butanol should be only faintly cloudy. A heavy cloudiness indicates the presence of sodium hydroxide. The yield then is lowered.

8. On standing, the ester slowly absorbs moisture and undergoes hydrolysis.

9. Dilute rather than concentrated acid is used since at least 12 ml. of water should be present. Some dissolves in the alcohol, some forms a hydrate with the barbituric acid, and some is needed to wet the solid. If the amount of water is insufficient, a collidal suspension is obtained when water is added later. An excess of acid is desirable, for the same reason. Check the concentration of the acid. Hydrometer measurements are quickest and sufficiently accurate.

10. The approximate solubilities of barbituric acid in 100 g. of solvent are: in water, at 26°, 1.1 g., and, at 0°, 0.3 g.; in butanol, at 26°, 0.07 g., and, at 0°, 0.01 g.

11. When the reaction mixture is allowed to stand too long (for a day or more), first a yellow and then a red color develops, and a red solid separates. In case the solution is darker than pale yellow, add activated carbon or alumina to the hot solution.

12. When washing with such small portions, the cold washing liquid should be added to the crystals and then both cooled again to 0° before filtering; otherwise, the water will become warmed instead of the crystals being cooled to 0°.

13. When crystallized from water, barbituric acid has 2 molecules of water of crystallization. The crystals effloresce.

14. Yield is 60%.

Questions

1. What two equations show the deleterious effect of sodium hydroxide?
2. What is the object of agitation, and what reaction is aided by not agitating?
3. What is formed when ethyl malonate reacts slowly with water?
4. What is the theoretical amount of 6 N hydrochloric acid required?
5. What are the principal components of the filtrate from the crude barbituric acid?
6. What is the main contaminant of the crude barbituric acid?
7. How does the weight of the crude product compare with that of the purified acid?
8. How do you account for a lower yield when the volume of butyl alcohol is less?
9. How strong an acid is barbituric acid?
10. Why is it an acid, rather than a base, as urea is?
11. Why is the melting point of barbituric acid not determined?
12. What commonly used drying agent cannot be used to dry butanol? Why? What drying agents can be used?
13. What are two reasons for the choice of an oil bath over a water bath in this case?

Experiment 27–3   Preparation of Urea (Woehler Synthesis)

Dissolve 0.05 mole of potassium cyanate (Notes 1 and 2) in 5 to 10 ml. of hot water, and add it immediately to a solution of 0.08 mole of ammonium sulfate in 15 ml. of hot water, preferably in a casserole to facilitate evaporation. Evaporate *rapidly* over a free flame until spattering occurs and then more slowly to dryness, taking care at the latter stage not to heat too strongly and thereby cause decomposition. This may safely be done by holding the casserole in the hand and keeping it in constant motion over the flame. If preferred, the final evaporation to dryness may be done over the steam bath. Grind the product to a fine powder, and again dry on the steam bath or in an oven at 100° for 10 to 20 minutes (Notes 3 and 4).

Extract the urea by heating the residue for 10 to 15 minutes with 15 to 20 ml. of hot absolute ethyl alcohol (Note 5) in a small (50-ml.) flask under a reflux condenser (Notes 6 and 7). Decant the liquid through a small fluted filter into a small beaker or evaporating dish, *and repeat the extraction at least once* with more solvent (Note 8). If the alcoholic extract is colored, add a pinch of decolorizing carbon (see 5.23), heat, and then refilter. Finally reduce the solution to about one third of its original volume, preferably by distillation, to prevent access of moisture. Allow to stand covered (Note 9).

Remove the crystals by suction (Note 10). A second crop may be obtained from the filtrate by further evaporation, followed by the addi-

tion of ether.   Determine the melting point and percentage yield (Note 11).

Notes

1. Potassium cyanate may be prepared by adding minium (red lead) Pb_3O_4 in small portions to a hot fusion of *anhydrous* potassium ferrocyanide and *anhydrous* potassium carbonate.   The reaction mixture may be used directly in the preparation of urea.   *Caution:* Wear goggles.

2. Potassium cyanate unless freshly prepared may contain potassium bicarbonate, owing to a reaction with water (cyanic acid is the nitrile of carbonic acid).

$$K^+ + O{=}C{=}N^- + 2H_2O \rightarrow K^+ + NH_3 + O{=}\underset{\underset{OH}{|}}{C}{-}O^-$$
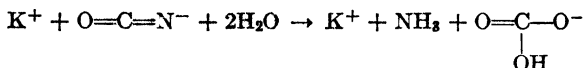
Old samples of the salt may have deteriorated so badly that little or no cyanate is present.   As a precautionary measure one should always test the cyanate for carbonate by adding a few drops of a solution of a barium salt to a solution of 0.1 or 0.2 g. of the cyanate in a few drops of water (barium cyanate is soluble).   If only impure cyanate is available, the carbonate may be precipitated by barium nitrate, the barium carbonate filtered off, and the filtrate used for the preparation of urea.   The amount of ammonium sulfate to be added can be calculated from the weights of potassium cyanate and dry barium carbonate.   The last can be dried rapidly by washing first with alcohol and then with ether.

3. Water should not be present; otherwise, inorganic salts may dissolve during the extraction.

4. The drying may be done in an oven, provided the temperature in the region of the dish does not exceed 100°.   Urea, if heated sufficiently, decomposes into ammonia and biuret.

5. If isobutyl alcohol is used in place of absolute ethyl alcohol, take 30 to 50 ml., or more, if necessary.   The extraction must be done rapidly, however, since at the higher temperature urea is likely to decompose.

6. Or instead of using a reflux condenser, the flask may be closed by a small watch glass and heated to about 70° on a water bath (not above the boiling temperature).

7. If the evaporation of the water was done quickly, the rearrangement reaction may not have reached equilibrium.   On this account the time of extraction should not be too short.

8. In case the amount extracted the second time is considerable, repeat once more. Urea is soluble, g. per 100 g., as follows: in water, 309 at 70°, 67 at 0°; in absolute ethyl alcohol, 20 at 70°, 2.6 at 0°; in n-propyl alcohol, 9.8 at 70°, 1.6 at 0°; in isobutyl alcohol, 5.7 at 70°, 1.0 at 0°.

9. If too much of the solvent is evaporated, the residue when warm is liquid urea in which some alcohol is dissolved.   When this solidifies later, it is less pure than if it had crystallized from solution.   If the evaporation is carried further and the temperature rises much above 100°, urea decomposes.

10. Since an additional crop can be obtained from the filtrate, it is important that it does not pick up impurities, as for example, from the inside of the Buechner funnel. If this is a possibility, it would be better to use a Witte filter plate in a glass funnel, and collect the filtrate in a small test tube with side arm.   (Refer to Figure 5–1F.) Take care that air is not sucked through, causing evaporation of solvent.

11. The melting point of urea is 132°.   The yield is 65 to 75%.

Questions

1. Is there evidence that hydrolysis has taken place during the preparation?
2. Assuming that no rearrangement or decomposition takes place during the evaporation, estimate the relative amounts of the salts present in the residue. Give reasons for your answer.
3. Can you explain why an excess of ammonium sulfate is taken?
4. Why is the aqueous solution evaporated rapidly?
5. Of what acid is urea the amide?
6. How may the two be converted into each other?
7. How is cyanic acid related to this acid?
8. What are the hydrolysis products of urea?
9. Show how urea enters into the nitrogen cycle in nature.
10. How is urea produced industrially?
11. What decomposition does urea undergo when heated?
12. What is the main impurity or impurities in the final product?
13. How can they be removed?

Experiment 27–4   Properties of Amides

A   SOLUBILITY.   Determine the approximate solubility of acetamide in water, ethanol, ether, ethyl acetate, benzene, carbon tetrachloride. Recall the solubility behavior of urea, Experiment 2–1.

B   HYDROLYSIS.   Try the action of 50–70% sulfuric acid (3 to 5 ml.), cold and hot, on 0.5 to 1 g. of acetamide. Note any volatile products. Add an excess of sodium hydroxide to the reaction mixture. Note any volatile products, heating if necessary. Repeat with urea and barbituric acid (Question 4).

C   SAPONIFICATION.   Try the action of 6 N sodium hydroxide (4 to 5 ml.), cold and hot, on 0.5 to 1 g. of acetamide. Note any volatile products. Add an excess of sulfuric acid to the reaction mixture. Repeat with barbituric acid and urea (see Question 4). In case there is no reaction hot, repeat, but use 1 to 2 g. of sodium hydroxide in 2 to 3 ml. of water, as in Experiment 26–2A (Note 1).

D   SODIUM NITRITE AND HYDROCHLORIC ACID.   Repeat Experiment 26–2B with acetamide, urea, and barbituric acid separately, in place of methylammonium chloride. Add more than 1 equivalent of hydrochloric acid. Note any change (Note 2). Make alkaline with sodium hydroxide (Note 3).

E   HYPOBROMITE.   Add 3 drops of bromine to 5 ml. of cold sodium hydroxide solution, and then add the resulting hypobromite solution to a dilute solution of urea.

F   BIURET FORMATION AND TEST FOR BIURET.   Heat about 0.5 g. of urea in a test tube with a small flame until a white opaque mass is

obtained.   The residue is a mixture of biuret and cyanuric acid.   When cold, boil with 5 ml. of water, cool, decant the aqueous biuret solution, and add to it 5 ml. of sodium hydroxide and one drop of a dilute solution of copper sulfate (Note 4).   Repeat, using an aqueous solution of a protein, as for example egg albumen, in place of the biuret solution.   Determine the limiting concentration that will give the test.

Notes

1. Recall results in Experiment 26–2A, and note any difference in rate.
2. Recall results in Experiment 26–2B.
3. The violet color with barbituric acid is due to the formation of a salt of violuric acid, the nitroso derivative of barbituric acid:

$$
\begin{array}{c}
\text{HO—C} = \text{N} \\
\text{O} = \text{N—C} \quad \text{C—OH} \\
\text{HO—C—N}
\end{array}
$$
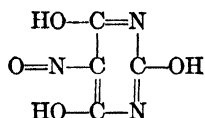
The color is discharged on acidification.

4. The soluble reddish color is due to a complex of cupric ion with biuret.   The test is given also by proteins, which contain the group NH_2—C—CONH—C—CONH, and by certain other compounds.

Questions

1. How do you account for the solubility behavior of acetamide?
2. Write equations for reactions in B, C, D, and E.
3. Does acetamide resemble an ester in any of its chemical properties?   Explain.
4. Do urea and barbituric acid differ in ease of hydrolysis or of saponification?
5. Explain why you might expect the two compounds to behave differently.
6. How do amides and primary amines differ in their behavior toward dilute hydrochloric acid?
7. Ditto, cold aqueous sodium nitrite and hydrochloric acid?
8. Explain how sodium hydroxide can be used to distinguish acetamide from methylammonium chloride?
9. What is the difference between an amide and an imide?
10. What is the formula of biuret?
11. Explain how urea can be determined quantitatively with sodium hypobromite.

Chapter 28

NITRILES

Nitriles may be obtained by: (a) the metathesis of inorganic cyanides with alkyl halides or alkali alkyl sulfates, (b) the dehydration of aldoximes with acetic anhydride, (c) the dehydration of amides with a powerful dehydrating agent, such as phosphorus pentoxide or phosphorus pentachloride, (d) heating amides with anhydrous aluminum chloride.

(a) $$C_2H_5I + NaCN \rightarrow C_2H_5CN + NaI$$

$$C_2H_5KSO_4 + KCN \rightarrow C_2H_5CN + K_2SO_4$$

(b) $$CH_3CH{=}NOH + (CH_3CO)_2O \rightarrow CH_3CN + 2CH_3COOH$$

(c) $$CH_3CONH_2 + P_2O_5 \rightarrow CH_3CN + 2HPO_3$$

(d) $$CH_3CONH_2 + AlCl_3 \rightarrow CH_3CONHAlCl_2 + HCl$$

$$CH_3CONHAlCl_2 \rightarrow CH_3CN + HCl + AlOCl$$
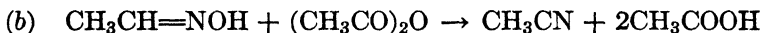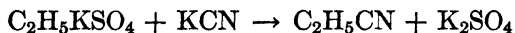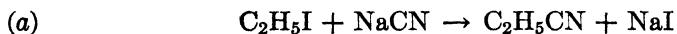
28.11 Alkyl Halides and Sodium (Potassium) Cyanide. Method *a* is the usual method of preparing nitriles because of convenience and cost. Silver cyanide cannot be used since it yields mainly the isonitrile. Generally the operation is carried out by refluxing the two reactants in an aqueous alcoholic solution. The mixed solvent has the advantage that it dissolves both reactants. Relative rates of alkyl halides are in the order: Iodides > bromides > chlorides. The reaction is rather slow, usually requiring 0.5 to 1 day with higher alkyl bromides such as *n*-butyl bromide. Sometimes potassium iodide is added when an alkyl chloride is used, since the reaction proceeds more rapidly through the intermediate formation of the corresponding alkyl iodide. Primary halides give yields of 60 to 70%, secondary halides give yields of 20 to 30%, and tertiary halides are converted to olefins by this treatment. The preparation of benzyl cyanide (Experiment 37–1) is an example of this procedure.

When the reaction is carried out with an alkyl potassium sulfate and potassium cyanide (or other suitable salt), the two dry solids may be heated to a fairly high temperature and the nitrile driven out, provided it is volatile. Disadvantages arise from the fact that alkyl potassium

sulfates decompose to olefins if heated to too high a temperature and from the heterogeneous character of the reaction. Sometimes the reaction of the alkyl potassium sulfate and potassium cyanide is carried out in a hot aqueous solution.

28.12 Dehydration of Oximes. In method *b* the oxime and acetic anhydride are heated. If the nitrile has a low molecular weight, it distils out. If it has a high molecular weight and boils above acetic acid, it is not very soluble in water, and the reaction product is separated by pouring the reaction mixture into water. The method is convenient for converting an aldehyde, through the oxime, to the nitrile.

28.13 Dehydration of Amides. In method *c* the amide is heated with phosphorus pentoxide, and the nitrile is distilled as formed. Method *c* is much used, since amides usually can be prepared from the acids readily. The cost of phosphorus pentoxide makes the method an expensive one. However, satisfactory yields are obtained with much less than the theoretical amount of phosphorus pentoxide, as the results in Experiment 28–1 show. This seems to indicate that metaphosphoric acid also is a dehydrating agent.

The removal of water from oximes (method *b*) is accomplished more easily than the removal of water from amides (method *c*), acetic anhydride sufficing in the first case, but phosphorus pentoxide being necessary in the second. Moreover, a higher temperature is possible with the second reagent since phosphorus pentoxide and metaphosphoric acid sublime only above 250°. Calculation of ΔH from bond-energy and resonance-energy values gives, for the gas-phase dehydration of an oxime, -45 kcal., and for the dehydration of an amide, $+20$ kcal. It is evident that a more powerful dehydrating agent is needed for the dehydration of amides.

28.14 Decomposition of Amides with Aluminum Chloride. Method *d* is carried out by heating a mixture of an amide with the double salt of sodium chloride and *anhydrous* aluminum chloride. Hydrogen chloride is evolved in two steps. After the initial evolution ceases, the flask is heated more strongly and the nitrile is driven over as formed, along with hydrogen chloride.

Experiment 28–1   Preparation of Acetonitrile (Methyl Cyanide)

Quickly weigh 15 to 30 g. of phosphorus pentoxide (in 5- or 10-g. portions, each on a clean sheet of smooth paper, not filter paper) and *quickly* transfer (use care not to drop on the skin) each portion to a 200-ml. distilling flask or a wide-neck extraction flask (Notes 1 and 2). Add ⅓ mole of *dry* (Note 3) pulverized acetamide and mix *thoroughly* by shaking. Connect to a short (25 to 30 cm.) condenser and wipe out any phosphorus pentoxide from the neck of the flask before inserting the stopper. Heat the flask with a small luminous flame kept in constant motion. After the first period of foaming is over, the flame may be increased and the product distilled. Collect in a test tube, small flask, or preferably in a small separatory funnel. Since it is desirable to know the amount obtained at this point, weigh the receiver beforehand.

To the distillate add one fourth to one fifth its volume of distilled water (Note 4) and then, while agitating and cooling in ice water, add, at first a little at a time, solid potassium carbonate (fine powder) until the aqueous layer is saturated (about 9 g. to each 10 ml. of water added). After settling, decant the liquid into a *small* separatory funnel, and draw off the lower aqueous phase. Shake the organic liquid with more potassium carbonate (refer to 12.28). Pour the organic liquid out of the top of the funnel into a small (25-ml.) distilling flask. Add 1 to 2 g. of phosphorus pentoxide and a few boiling chips. Distil with a *small* flame through a short *dry* condenser into a weighed bottle, collecting over a 3° or 4° range near the boiling point of acetonitrile. Calculate the percentage yield (Note 5).

Notes

1. If a wide-neck Soxhlet extraction flask is used, the pentoxide can be weighed *directly* into it. This facilitates the weighing process. Close the flask at once.

2. The neck of the bottle from which the pentoxide was taken should be wiped with a dry cloth before the stopper is reinserted in order to remove the adhering pentoxide. Any pentoxide spilled should *at once* be washed up (wet sponge or wet towel), not wiped up with a dry towel.

3. If the amide appears wet, it should be dried (Experiment 27–1).

4. The product usually contains some acid. This will not react with a dry reagent, such as dry potassium carbonate. On this account water must be added. If the amount of water is too small, the acid does not react. This entails some loss since this low-molecular-weight nitrile is quite soluble in water. Saturation with potassium carbonate decreases the loss from this cause.

5. The yield is 60% with 15 g. of phosphorus pentoxide and 70% with 30 g.

Questions

1. Which reactant is in excess? Why?
2. What was the loss in weight between the first crude distillate and the final product?
3. What caused this loss mainly? Explain.
4. If a sufficiently powerful catalyst were available, do you believe that acetamide would decompose into acetonitrile and water at room temperature? Explain.
5. What is the main impurity or impurities in the crude and final products?
6. State the steps taken to remove them.

Experiment 28–2   Properties of Acetonitrile

A   ACID HYDROLYSIS.   Place about 0.5 ml. of acetonitrile in a test tube with 3 to 5 ml. of 70 to 75% (by weight) sulfuric acid. Let stand for about 5 minutes, loosely stoppered, in water at 60° to 70°. Boil. Note any products. Cool, then add 4 to 5 g. of sodium hydroxide, and boil. Note any other products (Note 1).

B   ALKALINE HYDROLYSIS.   Put about 0.5 ml. of acetonitrile in a test tube with 1 to 2 g. of sodium hydroxide and 2 to 3 ml. of water. Let stand for about 5 minutes, loosely stoppered, in water at 60° to 70°. Boil. Note any products. Cool, then add 2 ml. of concentrated sulfuric acid, and boil. Note any other products (Note 2).

C   REDUCTION.   In a test tube place 0.2 to 0.3 g. of acetonitrile and 4 to 5 ml. of absolute alcohol; add four or five small pieces (about 3-mm. cubes) of metallic sodium (0.3 to 0.4 g.). If the mixture does not become warm, apply heat. Note any products.

Notes

1. Recall results in Experiment 27–4E.
2. Recall results in Experiments 26–2A and 27–4C.

Questions

1. Write equations for the reactions in A, B, and C.
2. Which product is more easily detected in A? in B?
3. Why is CH_3CN called acetonitrile? Write the classical valence structures and the electronic structures of methyl cyanide, methyl isocyanide, methyl cyanate, methyl isocyanate, methyl thiocyanate, and methyl isothiocyanate.
4. Show how ΔH may be calculated for the gas-phase reaction when a nitrile is formed from an amide.
5. Ditto, an oxime.
6. Calculate approximately the maximum amount of acetic acid that would be liberated if to the solution in B sulfuric acid were added to a phenolphthalein end point instead of the 2 ml. being added.
7. Ditto, to a bromphenol blue end point.

Chapter 29

AROMATIC HYDROCARBONS

Aromatic hydrocarbons may be prepared by eliminating certain groups present in aromatic compounds, or by attaching side chains to an aromatic hydrocarbon. Groups on side chains, such as halogen and hydroxyl, can be eliminated to yield saturated or unsaturated hydrocarbons, by the methods described for aliphatic hydrocarbons (see Chapters 13, 14, and 15).

The groups on the nucleus that can be eliminated are: (a) halogen, by reduction, (b) the carboxyl group, by alkali fusion, (c) the sulfonic acid group, by hydrolysis, (d) the amino group, through the diazonium salt, by reduction, (e) the hydroxyl group, by heating with zinc dust.

(a) $$H_2 + C_6H_5Br \xrightarrow{Pt} C_6H_6 + HBr$$

$$Mg + C_6H_5Br \longrightarrow C_6H_5MgBr$$

$$HCl + C_6H_5MgBr \longrightarrow C_6H_6 + MgBrCl$$

(b) $$NaOH + C_6H_5COONa \longrightarrow C_6H_6 + Na_2CO_3$$

(c) $$H_2O + C_6H_5SO_2OH \longrightarrow C_6H_6 + H_2SO_4$$

(d) $$NaNO_2 + 2HCl + C_6H_5NH_2 \longrightarrow C_6H_5N_2Cl + NaCl + 2H_2O$$

$$C_2H_5OH + C_6H_5N_2Cl \longrightarrow C_6H_6 + CH_3CHO + N_2 + HCl$$

(e) $$Zn + C_6H_5OH \longrightarrow C_6H_6 + ZnO$$
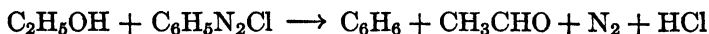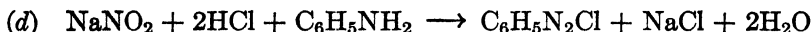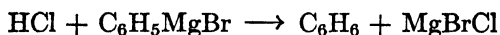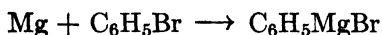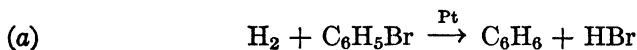
Aliphatic side chains may be attached to the aromatic nucleus by: (f) the Grignard reaction, (g) the Friedel–Crafts reaction, (h) condensation with an olefin, (i) the Wurtz–Fittig reaction, (j) the Clemmensen reduction of ketones.

(f) $$C_6H_5MgBr + BrCH_2CH=CH_2 \longrightarrow$$

$$C_6H_5CH_2CH=CH_2 + MgBr_2$$

$$C_6H_5MgBr + C_2H_5OSO_2C_6H_4CH_3 \longrightarrow$$

$$C_6H_5C_2H_5 + CH_3C_6H_4SO_3MgBr$$

(g) $\qquad$ $C_6H_6 + C_2H_5Cl \xrightarrow{\text{AlCl}_3} C_6H_5C_2H_5 + HCl$

(h) $\qquad$ $C_6H_6 + CH_2\!\!=\!\!CHCH_3 \xrightarrow{\text{H}_2\text{SO}_4} C_6H_5CH(CH_3)_2$

(i) $\quad$ $C_6H_5Br + 2Na + Br(CH_2)_3CH_3 \longrightarrow$

$$C_6H_5(CH_2)_3CH_3 + 2NaBr$$

(j) $\quad$ $C_6H_5COCH_3 + 2Zn + 4HCl \longrightarrow$

$$C_6H_5CH_2CH_3 + H_2O + 2ZnCl_2$$
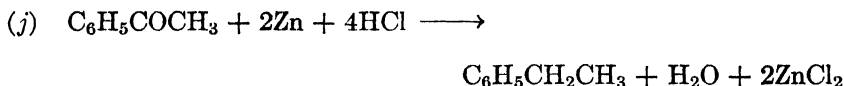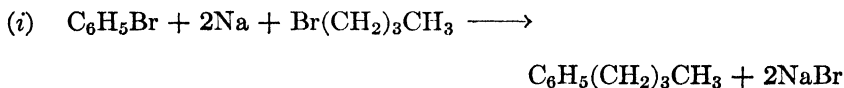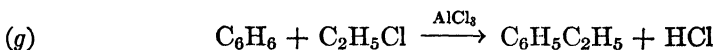
The removal of nuclear substituents, although not important for the preparation of hydrocarbons, which usually are more readily obtained in other ways, often is useful in the preparation of derivatives.

29.11   Elimination of Groups.   In method a elimination of halogen can be accomplished by the action of hydrogen over a palladium or platinum catalyst at room temperature or through the Grignard reagent. Elimination of carboxyl and hydroxyl groups, methods b and e, is effected merely by heating strongly with the respective reagent.   Elimination of the sulfonic acid group, method c, is accomplished by heating (150° to 200°) with water or with aqueous sulfuric acid.   Elimination of the amino group, method d, is discussed in Chapter 34 as one of the reactions of aromatic diazonium compounds.

29.12   The Grignard Synthesis.   Method f for the preparation of an unsaturated hydrocarbon makes use of the high reactivity of allyl bromide, and for a saturated hydrocarbon the reactivity of alkyl sulfates (usually methyl or ethyl) or of alkyl sulfonates, which are more reactive than the corresponding halogen compounds.

29.13   The Friedel–Crafts Synthesis.   Method g is one of the most useful.   In this an aliphatic halogen compound, or an aromatic compound in which a halogen atom is attached to an aliphatic side chain, reacts in the presence of a small amount of anhydrous aluminum chloride with an aromatic hydrocarbon or a suitable derivative, eliminating hydrogen halide.   If the reactants are benzene and an alkyl halide, the product is an alkylbenzene.

Agitation is necessary because of the heterogeneous nature of the reaction mixture.   Usually there are two liquid phases after some time, and eventually all of the solid usually disappears.   The lower liquid contains complex addition compounds of aluminum chloride with the alkyl halide, hydrogen chloride, and aromatic hydrocarbons.   The reaction takes place mainly in this heavier liquid phase.   The relative rates with which alkyl halides react in general are in the following order:

Fluorides > chlorides > bromides > iodides, and tertiary > secondary > primary.

The best catalyst for the Friedel–Crafts reaction is anhydrous aluminum chloride (or bromide). All reagents must be dry. The catalyst may be tested by heating some in a test tube. It should sublime easily. Any material that does not sublime probably is aluminum oxide, resulting from decomposition of any hydrated salt into the oxide and hydrogen chloride. Only a small amount of aluminum chloride is necessary in the preparation of hydrocarbons. (However, compare with Chapter 36.) Many other substances catalyze this reaction, for example boron trifluoride, anhydrous gallium trichloride, anhydrous stannic chloride, anhydrous ferric chloride, anhydrous zinc chloride, and amalgamated aluminum plus hydrogen chloride. These are not such good catalysts as aluminum chloride. However, an advantage of stannic chloride is the fact that it is a liquid.

For preparing monoalkylated benzenes, a large excess of benzene should be present, so as to minimize the formation of di- and higher alkylated benzenes, since subsequent alkylations also take place. Methyl and ethyl halides yield toluene and ethylbenzene, respectively. However, with higher primary alkyl halides isomerization takes place so that the benzene ring becomes attached to a secondary carbon atom, or to a tertiary, if one is present. Therefore, except in the case of toluene and ethyl benzene, the Friedel–Crafts synthesis as usually carried out does not yield 1-phenylated alkanes. The isomerization may be retarded by working at 0°, but mixtures usually result. Thus isoamyl chloride yields three hydrocarbons, namely, isoamylbenzene, α,β-dimethyl-*n*-propylbenzene, and *tert*-amylbenzene.

When a second alkyl radical is introduced into the molecule, the product first formed usually is a mixture, mainly of the *meta* and *para* isomers. On standing a long time, or on heating, the *meta* isomer predominates. This often is the main product when the reaction is carried out hot. When a third alkyl radical enters, the product is mainly the 1,3,5-isomer when much aluminum chloride is present.

Anhydrous aluminum chloride may cause detachment of groups already present, especially if hydrogen chloride is present, since the reaction is reversible. Thus toluene is converted into a mixture of benzene, xylene (mainly the *meta* isomer), and higher hydrocarbons, probably through a mechanism involving methyl chloride since hexamethylbenzene is converted into methyl chloride and a mixture of penta-, tetra-, tri-, and dimethylbenzenes. Similar complications are liable to arise in any Friedel–Crafts synthesis.

Radicals that retard substitution on the benzene ring (*meta*-directing radicals) retard the Friedel–Crafts reaction also. Nitrobenzene, aceto-phenone, and benzoic acid do not react at all. Thus, nitrobenzene may be used as a solvent for a Friedel–Crafts reaction. In Experiment 36–1, acetophenone is obtained in good yield from benzene and acetyl chloride, since the acetophenone does not react further. On the other hand, radicals that markedly activate the benzene ring, as for example meth-oxyl and dimethylamino, cause greater reactivity in the Friedel–Crafts reaction; two or more alkyl groups may be readily attached, even if a *meta*-directive radical is present. Alkyl radicals alone cause some deactivation.

Alcohols also react with benzene in the presence of anhydrous alu-minum chloride to form hydrocarbons. The reaction is slower than with an alkyl halide. More aluminum chloride is necessary, more than 1 mole of catalyst per mole of alcohol.

29.14 Condensation of an Olefin with an Aromatic Compound. Method *h* has become an important industrial process. Ethylene con-denses with benzene at 70–90° in contact with anhydrous aluminum chloride and at 25° with boron fluoride. Higher olefins in general react more rapidly than ethylene. Propylene or a higher homolog (ethylene requires much higher temperatures) condenses with benzene in contact with 96% sulfuric acid at temperatures as low as 0°.

29.15 The Wurtz–Fittig Synthesis. Method *i*, in which metallic sodium reacts with halogen compounds, was developed by Wurtz for synthesis of methane homologs, and by Fittig for synthesis of benzene homologs. Pure aromatic hydrocarbons having normal side chains can be obtained, for no rearrangement takes place, in contrast to condensa-tion with alkenes and the Friedel–Crafts synthesis. The reaction usually is carried out with bromides, for these are more reactive than chlorides and much cheaper than iodides.

The reaction is strongly exothermic. It can be shown that ΔH is *ca.* −170 kcal., by calculation from bond energies and the molal heat of formation of solid sodium bromide from metallic sodium and gaseous bromine. However, as usually carried out in the presence of a solvent, there is little danger of the reaction getting out of control, even when all reactants are present initially, because of the heterogeneous nature of the reaction mixture.

The rate of reaction depends in part on the concentration of the halogen compounds but mainly on the surface area of the metallic sodium. A solvent, usually an ether, is added to keep the mixture fluid otherwise, the mixture cannot be agitated owing to the voluminous nature of the sodium halide formed. Too much solvent should be

avoided, on account of lowered rate. The most effective way of increasing the rate is to increase the surface area of the sodium.

Reactive forms of sodium are: very thin shavings, "bird-shot" sodium, and fine wire. Shavings, if very thin, that is, about 0.1 mm. in thickness are quite satisfactory and have the advantages that a press is not necessary, as in the case of wire, and manipulation is simpler, compared to the shot. The shot is prepared by heating metallic sodium and xylene under a reflux condenser in a flask until the sodium melts. Then the flask is closed with a well-fitting stopper and given a few vigorous shakings while cooling, so that the sodium solidifies in a finely divided state. If shaken too much, the shot clumps together. The xylene must be removed thoroughly by decantation and by washing with anhydrous ether, unless it can be separated easily from the product. Shot has the disadvantage that it settles to the bottom of the reaction vessel and offers less surface than wire or thin shavings. Fine sodium wire and very thin shavings (see Experiment 29–1) usually give the best results.

Ethers in general are the best solvents for the Wurtz–Fittig reaction. The solvent in the butylbenzene experiment is absolute isopropyl ether. This has the advantage of a moderately high-boiling point, 68°, which permits the reaction to proceed at a satisfactory rate and yet under control. Another advantage of isopropyl ether is the ease with which it can be freed of alcohol (isopropyl) and water. The alcohol is removed by extracting with 6 N hydrochloric acid, and the water simply by fractional distillation through an efficient column, since it is a component of an azeotropic mixture (b.p. 60°). A disadvantage of isopropyl ether is its tendency to form peroxides. These must be removed if the distillation is to be carried to dryness (see Experiment 19–5, Note 10).

When an unsymmetrical hydrocarbon is being prepared, as for example n-butylbenzene (Experiment 29–1), side reactions occur between like halides. From a statistical point of view, symmetrical hydrocarbons constitute 50% of the reaction product, if the rates of all three reactions are the same. Actually, the coupling reactions of an aryl halide with its self by metallic sodium usually is the slowest of the three.

Another type of side reaction is the alkylation of ether, if it is employed as the solvent:

$$C_3H_7OC_3H_7 + C_4H_9Br + 2Na \rightarrow C_3H_7—C_4H_9 + C_3H_7ONa + NaBr$$
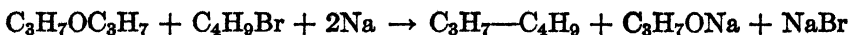
29.16 Biphenyl Coupling. When two aryl groups are to be coupled so as to produce biphenyl or a substituted biphenyl, better results are obtained by replacing metallic sodium with copper powder or copper bronze. For this iodides are preferred, but bromides also are used. Copper is especially useful for coupling compounds containing one or

more nitro groups in addition to the halogen atom. Copper does not affect the nitro groups, whereas metallic sodium brings about profound changes, owing to its strong reducing action. The reaction mixture must be strongly heated when copper powder is used.

29.17 The Clemmensen Reduction. In method *j* ketones are reduced to hydrocarbons by refluxing with hydrochloric acid and amalgamated zinc. The acid concentration may vary. A suitable organic solvent (alcohol) may be added to increase the solubility of the ketone. This method, in conjunction with the Friedel–Crafts synthesis of aromatic ketones (Chapter 36) is valuable for attaching a higher normal aliphatic chain to an aromatic nucleus.

Experiment 29–1   General Method of Preparing Alkylbenzenes, by the Wurtz–Fittig Synthesis

n-Butylbenzene (Note 1)

Free about 400 ml. of isopropyl ether of any isopropyl alcohol by shaking several times with 6 *N* hydrochloric acid (Note 2). Then shake it with sodium carbonate solution until it is neutral to moist litmus paper, and separate it from the aqueous phase in a separatory funnel. Remove most of the dissolved water as part of the constant-boiling mixture (b.p. 59–60°) by means of fractional distillation through an efficient fractionating column. After the temperature has risen to that of isopropyl ether (b.p. 67°), remove any condensed water from the condenser and upper part of the fractionating tube before collecting the dry isopropyl ether (Note 3). Collect about 200 ml. in a dry round-bottom flask, discarding the first 15 or 25 ml. Do not distil to dryness, because of danger of an explosion due to possible peroxide.

Weigh out a piece of metallic sodium of moderate size (8 to 12 g.; Note 4), and cut this into *very thin* shavings 0.2 mm. or less in thickness (Note 5), *Caution* (Experiment 15–1, Note 10), *putting each shaving into the ether as soon as cut.* Continue until 1 g. atomic weight of metallic sodium has been cut (Note 6). While the sodium is reacting with the small amount of water remaining in the ether, attach a dry reflux condenser (refer to 7.23), making sure that water cannot leak into the flask.

To the mixture of anhydrous isopropyl ether and sodium add a mixture of 0.4 mole each of anhydrous bromobenzene (Experiment 30–1) and anhydrous *n*-butyl bromide (Note 7 and Experiment 16–1), and mix thoroughly. If the sodium has been properly prepared, the liquid should boil within a few minutes and continue boiling for about 0.5 hour. If the reaction becomes too vigorous, cool moderately. Keep the mixture

boiling by means of an oil bath until the total time of heating is *ca.* 1 hour if the sodium was properly prepared, and much longer (2 to 4 hours) if otherwise. It is desirable to let the reaction mixture stand overnight. An occasional vigorous shaking helps to remove the crust of sodium bromide from the surface of the sodium. In case the reaction mixture must stand for some time after this, drain the water from the condenser as a precaution. Separate *n*-butylbenzene from unreacted sodium in one of the two ways described in the following (Note 8).

1. Carefully decant the liquid phase through a fluted filter paper from the solid, or use suction filtration (*Caution:* no flame near during the entire process), and wash the solid twice with 25 to 35 ml. of isopropyl ether. Add the washings to the main portion. Strip off the isopropyl ether by fractional distillation. Use preferably a short efficient column having small holdup attached to a flask of the proper capacity to hold satisfactorily the expected amount of product (Notes 9 and 10). Make cuts, in case the intermediate fractions are significant in amount, and subject these to systematic fractionation by cuts (Subsection 9.13). Collect *n*-octane and any unchanged bromobenzene separately. Finally, remove the column, and, using a small condenser or merely the side arm of the flask (refer to 7.21), collect *n*-butylbenzene in a 5° range near the boiling point. Calculate the percentage yield (Note 11). Decompose the residual metallic sodium by adding alcohol in *small* portions with shaking and cooling until 30 to 50 ml. have been added or until the reaction is quite slow; then add water at first in *small* portions and with shaking until all of the sodium has reacted.

2. Decompose the sodium with alcohol and distilled water (Note 12) as described in method 1 while it is in contact with the organic phase. Separate the two phases; shake the organic phase four or five times with water, and filter through dry filter paper in case the water does not separate readily and completely. Distil as in method 1. If preferred, most of the dissolved water can be removed with a suitable drying agent, but it is simpler to remove this by distillation, as done earlier.

Test the product for bromine as follows: To about 1 ml. of butylbenzene in a test tube add a piece of sodium metal, pea size, and warm gently. When the sodium melts, shake well, and keep the sodium melted while agitating gently for 1 to 2 minutes. Cool, add alcohol carefully, and, when the sodium has reacted, acidify with c.p. nitric acid. Add aqueous silver nitrate. In case the test is positive, heat the entire amount of butylbenzene carefully with metallic sodium, in a flask with air condenser attached, agitating thoroughly for *ca.* 5 minutes, while the sodium is molten. Remove excess sodium, dry, and distil.

Notes

1. n-Amylbenzene and isoamylbenzene can be prepared satisfactorily by this procedure from n-amyl and isoamyl bromide, respectively, but yields of isobutylbenzene, using isobutyl bromide, are very low. For ethylbenzene use ethyl iodide when isopropyl ether is the solvent or ethyl bromide with absolute ethyl ether. In this case the reaction is much slower, and the mixture should stand for a few days. The propylbenzenes boil very close to bromobenzene (156°).

2. This procedure is necessary when the presence of the alcohol is suspected.

3. The residual ether, even though dry, is not satisfactory without being distilled, probably because of the presence of organic peroxides (*Caution:* Experiment 19–5, Note 10).

4. Preferably use dry sodium; if it has been kept under kerosene, the liquid should be well removed by filter paper. Any crust of oxide should be trimmed off.

5. Use a *sharp* thin-bladed knife, and start the cut on the side of the piece of sodium, below the upper surface. In this way a thin paper-like sheet of sodium can be obtained. It is important that the sodium be in *very* thin slices, since this is a heterogeneous reaction (see 29.15).

6. Other satisfactory forms of sodium are wire, by the use of a sodium press, and "bird-shot" sodium (see discussion).

7. Or use an equivalent amount of n-amyl bromide, isoamyl bromide, or other alkyl halide, in case some other hydrocarbon is to be prepared. The effect of varying the ratio of alkyl to aryl halide may be studied by qualified students; also the effect of adding a small amount (1 to 5 g.) of some other substance (ethyl acetate, acetonitrile), which is said to aid the reaction.

8. The first procedure has the advantage that the liquid is anhydrous. It has the disadvantages that the filtration is slow, recovery of biphenyl is very poor, and sometimes the filtrate contains sodium compounds which separate as the distillation proceeds and which may cause some decomposition as the residual liquid, mainly the desired product, becomes small in volume. The second procedure has the advantage that inorganic materials are well removed, but the disadvantages that more time is required before distillation can be undertaken and that the liquid contains water.

9. The usual danger of distilling isopropyl ether solutions to dryness is absent, because the peroxide is destroyed by metallic sodium. However, it re-forms on standing in contact with the air. For that reason the liquid should be distilled without needless delay, after separation from the metallic sodium.

10. An efficient Vigreux column or a long-packed column may be used during the removal of the isopropyl ether and perhaps also of the octane and bromobenzene. Then the residue should be distilled from a small apparatus, the column and flask being rinsed out with ethyl ether. The subsequent distillation must be done slowly. Refer to 9.15.

11. Boiling points and yields are: n-butylbenzene, 183°, 55%; isoamylbenzene, 198°, 45%; n-amylbenzene, 205°, 45%.

12. Emulsification usually is more troublesome with "hard" water.

Questions

1. Explain how the ether is dehydrated by the distillation.
2. Why should the freshly cut pieces of sodium be placed in the ether as soon as cut?

3. Was there any evidence that other reactions besides the one to form butyl-benzene took place?

4. Why not add the bromides before the small amount of water has reacted with sodium metal?

5. Why is the water drained from the condenser?

6. What is the principal impurity in the final product?

7. What are the advantages of isopropyl ether over ethyl ether as a solvent for this preparation?

8. How do you think the following affect a solution of isopropyl alcohol in iso-propyl ether (a) 12 N HCl, (b) 6 N HCl, (c) 1 N HCl?

9. For what other reasons besides the possibility of encountering a troublesome emulsion do you think that method 1 is preferable to method 2?

10. Which organic bromide should be in excess? Give reason for your answer.

11. Which method would you select for the preparation of sec-butylbenzene? tert-butylbenzene? n-propylbenzene?

12. Show the calculation of ΔH in the n-butylbenzene synthesis from bond-energy values and the heat of formation of solid sodium bromide.

Experiment 29–2   General Method of Preparing Alkylbenzenes by the Friedel–Crafts Synthesis

sec-Butylbenzene (Note 1)

Equip a 0.5-liter three-necked flask with a sealed mechanical stirrer, dropping funnel, and reflux condenser. Be sure the apparatus is dry. To the condenser attach a calcium chloride drying tube and to this an apparatus for absorbing hydrogen chloride in water without danger of having water suck back into the reaction mixture.

Place 2 moles of dry benzene (Notes 2 and 3) and 0.05 mole of an-hydrous aluminum chloride (Note 4) in the flask. While stirring vigor-ously, allow 0.40 mole of dry sec-butyl chloride (Experiment 16–3) to flow into the flask during the course of about 1 hour, cooling if the temperature rises above 20°, and stopping the flow if the evolution of hydrogen chloride becomes too vigorous. Stir for 1 or 2 hours at 50°, or for about 5 hours at room temperature. The evolution of hydrogen chloride should be slight (Note 5).

Cool, and then pour the reaction mixture with vigorous stirring into a mixture of 50 ml. of 6 N hydrochloric acid and about 100 g. of ice (Notes 6 and 7). Separate the phases, and extract the aqueous phase once with benzene. Wash the combined benzene phase several times with water and then with dilute aqueous base until dissolved acid is removed (Note 8). Dry with potassium carbonate in stages. Strip off excess benzene and any unreacted sec-butyl chloride as described in Experiment 29–1, and collect the product in a 5° range. Calculate the percentage yield (Note 9).

Notes

1. Many hydrocarbons can be prepared by this general procedure, using primary, secondary, or tertiary alkyl halides (refer to 29.13). Sometimes the alkyl halide is added slowly to hot benzene. With tertiary chlorides, best results are realized by not heating, and by letting the reaction mixture stand a day or longer. With *tert*-butyl chloride (Experiment 16–4) toluene yields *m-tert*-butyltoluene, and *m*-xylene yields *tert*-butyl-*m*-xylene (1,3-dimethyl-5-*tert*-butylbenzene) in low yields.

2. The benzene and *sec*-butyl chloride must be anhydrous. Dry them by allowing them to stand overnight in an Erlenmeyer flask in the presence of anhydrous calcium chloride. Filtering through a plug of cotton removes the drying agent sufficiently well.

3. The yield is improved by increasing the amount of benzene, provided that, in its removal, no product is lost.

4. Test the aluminum chloride as described in 29.13. Make the calculation on the basis of $AlCl_3$.

5. *n*-Butyl chloride or bromide may be used instead. However, *sec*-butyl chloride is cheaper than either of these.

6. In case basic aluminum salts precipitate, more hydrochloric acid may be added.

7. The amount of ice can be larger, if desired.

8. Refer to Chapter 6 if an emulsion results.

9. Boiling points: *sec*-butylbenzene, 173°; *tert*-butylbenzene, 169°; *m-tert*-butyl-toluene, 185–187°; 1,3-dimethyl-5-*tert* butylbenzene, 205°. Yields: *sec*-butylbenzene, 60%; *tert*-butylbenzene, 45% after 4 days' standing.

Questions

1. Why is such a large excess of benzene taken?
2. What is the function of the aluminum chloride?
3. Explain why *sec*-butyl chloride is cheaper than *n*-butyl chloride or *n*-butyl bromide.
4. Explain why *tert*-butyl chloride is cheaper than isobutyl chloride.
5. What product do you predict to be formed if the *sec*-butyl chloride is replaced by *n*-amyl chloride?
6. How can *n*-butylbenzene be prepared?
7. Can *sec*-butylbenzene be obtained by a Wurtz–Fittig synthesis?
8. What are the probable impurities in the crude and final products?
9. What steps have been taken to remove them?

Experiment 29–3   Properties of Aromatic Hydrocarbons

A NITRATION.   To about 0.3 ml. of concentrated nitric acid add gradually, with some cooling, twice the volume of concentrated sulfuric acid. Add 2 drops of benzene, and agitate more or less continuously for 2 or 3 minutes. Stopper the tube loosely, and place it in water at 50° for 2 or 3 minutes, agitating at intervals. Cool, and pour the reaction mixture into five to ten times the volume of water (Note 1).

Repeat with ligroin (petroleum ether, b.p. above 80°) and with either toluene or some other benzene homolog, for example *n*-butylbenzene, *sec*-butylbenzene, *tert*-butylbenzene, or *m-tert*-butyltoluene (Notes 2 and 3).

B FRIEDEL–CRAFTS COLOR REACTION.   Place 0.2 to 0.3 g. of *anhydrous* aluminum chloride in a dry test tube, and heat strongly so that the aluminum chloride sublimes onto the walls. While the tube is still warm add 1 drop of benzene. Allow a small amount of chloroform vapor to enter the tube, as for example by tipping an open bottle of the liquid at the mouth of the tube. Then finally add 1 drop of chloroform. Note colors. Repeat with petroleum ether, toluene or *n*-butylbenzene, and naphthalene (Note 4).

Notes

1. Benzene and nitrobenzene are converted into solid *m*-dinitrobenzene.

2. Toluene is converted mainly into solid 2,4-dinitrotoluene. Other alkylbenzenes are converted to dinitro derivatives, which are heavier than water and usually are solid. Ligroin is not noticeably altered.

3. In case the product is not a solid, repeat, using 95% nitric acid (sp. gr. 1.5) in place of concentrated nitric acid. *Caution:* This acid is much more corrosive than concentrated nitric acid. Add the sulfuric acid, drop by drop, with cooling. Also, add the hydrocarbon, drop by drop, to the cooled mixture.

4. First, a Friedel–Crafts reaction takes place, with the formation of hydrogen chloride and triphenylmethane. The latter combines with aluminum chloride to produce a highly colored complex. Benzene and homologs and also aryl halides give orange to red colors, naphthalene gives blue, and biphenyl purple. Ligroin, unless carefully purified by shaking with fuming sulfuric acid, may give a color.

Questions

1. On what physical property does the nitration test depend for quickly differentiating an aromatic from an aliphatic hydrocarbon?

2. How can the nitration test be employed for differentiating one aromatic hydrocarbon from another?

3. How does the Friedel–Crafts color reaction differentiate an aromatic from an aliphatic hydrocarbon?

Chapter 30

AROMATIC HALOGEN COMPOUNDS

Aromatic halogen compounds are of two types. The halogen atom may be attached to the benzene nucleus or to a side chain. The former may be obtained by replacement of the diazonium group (this is discussed in Chapter 34) and the latter by the methods that are applicable to aliphatic halogen compounds (Chapter 16). Both types may be prepared by direct substitution.

$$C_6H_6 + Cl_2 \xrightarrow{I_2} C_6H_5Cl + HCl$$

$$C_6H_6 + Br_2 \xrightarrow{FeBr_3} C_6H_5Br + HBr$$

$$1,4\text{-}CH_3C_6H_4NO_2 + Br_2 \xrightarrow{FeBr_3} 1,2,4\text{-}CH_3C_6H_3BrNO_2 + HBr$$

$$2C_6H_6 + I_2 + 2HNO_3 \longrightarrow 2C_6H_5I + 2H_2O + 2NO_2$$

$$C_6H_5CH_3 + Cl_2 \xrightarrow[\text{light}]{\text{heat}} C_6H_5CH_2Cl + HCl$$
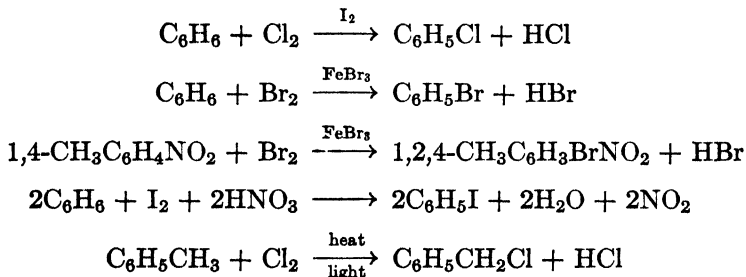
30.11 Thermochemistry. When for the gas-phase substitution reactions $-\Delta H$ is calculated by means of bond energies alone (resonance being neglected), the results are: for chlorination 24 kcal., for bromination 8 kcal., and for iodination (with molecular iodine) -6.5 kcal. The stabilization of the aryl halides (that is, the nuclear-substituted compounds) due to resonance might increase these values by 2 or 3 kcal. In the liquid-phase reactions, the heats of vaporization of reactants and products probably cancel out in the case of chlorinations. However, in brominations and iodinations, the afore-mentioned values probably are decreased a few kilocalories by the fact that only one compound, one of the products, is gaseous.

30.12 Rates. At room temperature and in the dark the rates are negligible. In the case of benzene, substitution is aided by the presence of a suitable catalyst. Satisfactory catalysts for the formation of chlorobenzene are: (a) mild catalysts: pyridine, iodine; (b) moderately active catalysts: anhydrous antimony pentachloride, anhydrous ferric chloride; (c) very active catalysts: anhydrous aluminum chloride. Often metallic iron or aluminum is added. The actual catalyst is then the

corresponding metallic halide. The hydrated forms have little or no catalytic effect. Bromobenzene formation is promoted similarly but in general is less rapid. However, it proceeds very rapidly in the presence of anhydrous aluminum bromide. Iodine in the absence of an oxidizing agent has little or no action on benzene.

Benzene homologs react similarly to benzene except that generally substitution in the ring is easier. However, in the absence of a catalyst which promotes nuclear substitution, the side chain is attacked. In the case of toluene, side-chain substitution becomes the predominating reaction in sunlight. Generally speaking, preferential chlorination or bromination on the side chain is favored not only by the absence of the nuclear-promoting catalysts and by illumination but also by heating. Side-chain substitutions are promoted also by the presence of sulfur or of phosphorus trichloride.

30.13 Nuclear Substitution. In the preparation of nuclear-substituted chlorine compounds, chlorine gas is passed into the mixture of hydrocarbon and the catalyst until the desired gain in weight is realized.

In the preparation of bromine compounds the desired amount of liquid bromine is added as in the preparation of bromobenzene (Experiment 30–1) and of 2-bromo-4-nitrotoluene (Experiment 30–2). If metallic iron is used, some little time is required for the formation of the actual catalyst, iron bromide. After that the reaction may become too vigorous unless the temperature is kept under control. The formation of dihalo compounds can be diminished by having the hydrocarbon in excess and by not using too active a catalyst.

Whereas an aliphatic side chain facilitates nuclear substitution somewhat, some other *ortho–para*-directing groups, as for example the hydroxyl group, so activate the *ortho* and *para* positions that no catalyst is necessary. In fact, substitution may proceed so readily that it is not possible to obtain good yields of monohalogenated compounds, owing to the fact that they are halogenated rapidly also. In such cases dilution with a suitable solvent usually gives satisfactory results. Acetic acid is one of the best solvents for this purpose. Others sometimes used are ethyl alcohol, ethyl ether, chloroform, and carbon disulfide. On the other hand, *meta*-directing groups decrease the ease of benzene substitution. Thus in the bromination of *p*-nitrotoluene much more iron bromide catalyst is needed than in the bromination of benzene. Anhydrous aluminum chloride and bromide catalyze so many other reactions that in some cases the iron salts give better results.

In the preparation of iodine compounds, substitution does not take place unless the reaction is rendered exothermic. This can be accomplished by adding an oxidizing agent, as for example iodic acid or nitric

acid, to the mixture of iodine and aromatic hydrocarbon. In the case of some very reactive compounds, the addition of alkali is all that is necessary.

30.14   Side-Chain Substitution. In the preparation of side-chain-substituted chlorination products, chlorine gas may be passed into the boiling hydrocarbon under a reflux condenser until the desired weight is reached. This procedure has certain disadvantages, as follows: (1) Chlorination proceeds beyond the mono stage; (2) the reaction temperature is limited to the boiling point of the reaction mixture; (3) the correct weight cannot be ascertained, because toluene passes out with the hydrogen chloride, and because higher chlorinated products are present.

Vapor-phase chlorination, as in the preparation of benzyl chloride (Experiment 30–3), can be carried out so as to circumvent these difficulties by: (1) keeping hydrocarbon in excess at all times, (2) permitting the reaction temperature to rise above the boiling point of the liquid, (3) determining the completion of the reaction by the boiling point of the reaction mixture. This is realized by the use of a chlorinating tube (Figure 30–1), for the reaction temperature can rise above the temperature of the boiling liquid, and the fractionating column prevents the higher-boiling chlorinated product from re-entering the reaction zone after having flowed out of it. Chlorination is continued until the boiling point of the liquid reaches that of the desired product.

Bromination of the side chain often is accomplished by running liquid bromine under the surface of the hot hydrocarbon slightly below the boiling temperature. Illumination is not always necessary, as in the preparation of α-bromo-o-xylene, where the bromination proceeds readily at 130°.

30.15   Recovery and Purification. Simple halogenated aromatic hydrocarbons usually are easily purified, for the hydrogen halide and excess halogen can be removed completely by water or aqueous bases (see Chapter 6 for breaking of emulsions, which may form here). Any unreacted hydrocarbon generally can be distilled away from the less volatile halogenated product. Solid halogen compounds usually can be purified by crystallization.

Experiment 30–1   Preparation of Bromobenzene

To a 500-ml. dry flask far enough above the desk top to permit a cooling bath to be slipped under it easily from the side, attach a dry reflux condenser. To this attach a device to permit good absorption of the evolved hydrogen bromide in 100 ml. of water without danger of having water suck back into the reaction mixture (Note 1). Place 1 or 2 moles of anhydrous benzene (Note 2) and 0.5 mole of anhydrous

bromine in the flask (*Caution: Make all bromine transfers in the hood;* see Experiment 14–1, Note 8), connect it to the apparatus, cool it in a bath of water at 15°, and drop in 0.001 or 0.002 g. atomic weight of iron filings (Note 3). Reaction should begin within a few minutes (Note 4). If it does not, remove the cold-water bath, and let the temperature of the flask increase slowly, either by heat from the hand or with a small flame. It should not be necessary to heat the liquid above 25°. After action has started (Note 5), immerse in a bath at 15°. After hydrogen bromide has been evolved actively for an hour, the mixture may be allowed to stand overnight without danger of the reaction becoming too vigorous. When the reaction is largely over (or at the next laboratory period), remove the bath, and heat the flask with a small flame until bromine vapor is no longer visible above the dark-colored liquid. Transfer the aqueous solution to the bottle marked "Crude Hydrobromic Acid" (Note 6).

Recover bromobenzene either by steam distillation (refer to Note 7) or by fractional distillation. In the latter case remove iron bromide completely and most of the hydrobromic acid by several washings with water (Note 8). Finally wash with aqueous sodium carbonate or hydroxide. Separate as completely as possible from the aqueous layer, dry with anhydrous potassium carbonate or calcium chloride, and filter into a suitable small distilling flask. Strip off the benzene without losing bromobenzene (Note 9). In case the separation is not sharp, collect fractions in the approximate ranges: 130–150°, 150–160°, 160–180°. Redistil these in systematic fashion (refer to 9.13) and narrow the limits of the middle fraction with succeeding fractionations. Collect finally the portion that distils within a range of 5°, and calculate the percentage yield (Note 10).

The residues boiling above 180° contain *p*-dibromobenzene. Recover this by crystallizing the residues from 20 to 30 ml. of alcohol, after refluxing for a few minutes with 0.5 to 1.0 g. of decolorizing carbon. Recrystallize until pure (Note 11).

Notes

1. Hydrogen bromide must not be allowed to escape into the laboratory.

2. Less dibromobenzene is formed, the larger the excess of benzene.

3. If filings are not available, add two or three iron tacks, the surfaces of which must be clean and bright. However, the reaction takes place more readily with iron filings. The resulting ferric bromide must remain anhydrous to retain its catalytic effect.

4. The first reaction is between bromine and iron, and this may be fast or slow, depending on the nature of the iron, its surface, and its state of subdivision. If the reaction is started at room temperature, more bromine is lost.

5. Small gas bubbles break at the surface of the reaction mixture, the gas space above is dark from bromine vapor, and striations appear in the water which absorbs the hydrogen bromide.

6. From these residues pure constant-boiling hydrobromic acid solution may be obtained by distillation. It can be used in other preparations, for example bromo-toluene, Experiment 34-1, Note 1.

7. Refer to Chapter 10. The operation may be carried out by passing in steam or, more simply, by adding much water and distilling. At first benzene steam distils very readily. This is collected separately. Then the distilling temperature rises to *ca.* 96° while bromobenzene steam distils more slowly. Continue until the organic phase crystallizes in the condenser. Change the receiver, and collect the dibromo-benzene separately. Redistil the bromobenzene after drying, and recrystallize the *p*-dibromobenzene.

Advantages of steam distillation over fractional distillation in this case are: (1) nonnecessity of removing hydrobromic acid, (2) avoidance of emulsion difficulties, (3) reasonably sharp separation of the three principal organic compounds from each other, (4) easy recovery of *p*-dibromobenzene. Sharper separation is possible by steam distillation through a fractionating column.

8. If the iron bromide is not removed completely before the alkaline solution is added, a bad emulsion may result, owing to the presence of insoluble iron hydroxide (refer to Subsection 6.16, Emulsions).

9. The distillation may be done from a Claisen flask having a *short* (2- to 5-cm.) packed fractionating column in the neck (refer to 9.15). Note that the greater the amount of packing, the greater the loss of product, since the packing will be wet with bromobenzene. Use of a longer column results in needless loss of bromobenzene.

10. The yield is 75%.

11. It may be desirable to add a *small* amount of water to the alcohol to aid crys-tallization. However, too much should not be added, because then an oil may separate, owing to the fact that the impurities become insoluble. *p*-Dibromobenzene crystallizes in colorless leaflets. It melts at 88° and boils at 219°.

Questions

1. What is the minimum volume of water necessary to dissolve the hydrogen bromide evolved?

2. What is the purpose of the iron filings?

3. What other substances could be used?

4. Why is the temperature kept low during the bromination?

5. Which reagent is in excess, and why?

6. What factors cut down the yield?

7. How could the yield be improved?

8. How could the loss of bromine be diminished?

9. Do bond-energy values apply to a gaseous or to a liquid system?

10. For this particular system is the actual ΔH different from the ΔH calculated from bond-energy values? Explain.

11. What would be the market value of the hydrobromic acid obtained in this experiment if it were in the form of the constant-boiling mixture?

12. Explain why steam distillation gives a sharper separation of benzene, bromo-benzene, and *p*-dibromobenzene than does fractional distillation.

13. What are the probable impurities in the product?

Experiment 30–2   Preparation of 2-Bromo-4-nitrotoluene

Attach a dry reflux condenser to a dry 500-ml. flask on a single movable stand, and set the flask high enough above the desk top to permit a hot-water or a steam bath to be moved under easily from the side. To the reflux condenser attach a device that permits good absorption of the evolved hydrogen bromide in 75 ml. of water without danger of sucking back (Note 1).   Place 0.30 mole of p-nitrotoluene and 0.3 mole of anhydrous bromine in the flask (Caution: Make all bromine transfers and weighings in the hood; see Experiment 14–1, Note 8), mix thoroughly, and cool to ca. 15°.

With cooling bath handy add 0.03 g. atomic weight of iron filings (Note 2), and attach the flask to the apparatus.   If there is no apparent reaction within 5 or 10 minutes (Note 3), heat the flask for ca. 0.5 minute with a very small flame.   As soon as the temperature of the flask at the bottom reaches 40° to 50° (owing to the reaction between iron and bromine), dip the flask in the cooling bath for a few seconds. Repeat at intervals.   After this reaction is well over, gently heat the contents.   Hydrogen bromide should be evolved (Note 3).   If the evolution of hydrogen bromide becomes too rapid, surround the flask with a cold-water bath, but do not cool it so far that the reaction becomes quite slow.   After a good evolution of hydrogen bromide has been observed for ca. 1 hour, and the evolution of hydrogen bromide has slackened, add 0.1 mole more of bromine, and mix thoroughly (Note 4).   Let stand 2 or 3 hours (Note 5).   Set the flask on a steam bath, and heat at 50° to 60°, gradually increasing the temperature as the evolution of hydrogen bromide decreases, but taking care not to drive over much bromine.   It may be 2 or 3 hours before action ceases.   Later transfer the aqueous solution of hydrogen bromide to a bottle marked "Crude Hydrobromic Acid" (Note 6).

While the flask and contents are still hot, disconnect the absorbing apparatus, and carry the flask and condenser to the hood.   Disconnect the flask and pour in about 200 ml. of warm water.   Heat until the solid melts, and then thoroughly agitate the contents.   Set the flask in cold water so that the contents will form a solid cake.   Pour off as much of the water phase as possible.   Repeat two or three times so as to remove most of the hydrobromic acid (Note 7).   Heat again, pour the contents into a large procelain mortar (hood), and, when cold, add a solution of 10 to 20 g. of sodium bisulfite or sodium metabisulfite in cold water, and grind the mixture until the bromine is removed, breaking up all lumps, and repeating if necessary.   Filter with suction onto a Buechner funnel (Note 8), wash well with water, stir the solid (preferably in a

beaker), with 20 to 25 ml. of cold alcohol to remove most of the organic impurities, and filter again with suction, avoiding needless evaporation of the solvent (refer to 5.42). Wash with a small amount of alcohol.

Crystallize the crude product from 200 to 400 ml. of hot alcohol (Note 9), after having added some decolorizing carbon (refer to 5.23). Take care that an oil does not form (refer to 5.24, 5.31, and 5.33). Let stand until crystallization is complete.

Obtain a second crop from the filtrate. Determine the melting point of each crop, and calculate the percentage yield (Note 10).

Notes

1. Hydrogen bromide must not be allowed to escape into the laboratory.

2. The first reaction is between bromine and iron. This may be fast or slow, depending on the nature of the iron, its surface, or its state of subdivision. The resulting ferric bromide must remain anhydrous to retain its catalytic effect.

3. Bubbles rise from the reaction mixture, and striations appear in the water which absorbs the hydrogen bromide.

4. It may be desirable to add even more, up to 0.2 mole of bromine, depending on how much is lost. However, the yield drops if too much is added.

5. It is better to let the mixture stand overnight. Replace cork stoppers with rubber stoppers. Cork disintegrates badly in contact with hydrogen bromide.

6. Pure constant-boiling hydrobromic acid may be obtained by fractional distillation of this crude acid.

7. Time can be saved by decanting the warm aqueous phase from the heavy oil. More product is lost this way. The loss can be minimized by decanting through a filter paper, which should be heavy, to avoid breaking, and should be previously wet with water, to hold the oil.

8. Use pressure to remove as much of the liquid as possible and to prevent formation of cracks (refer to Subsection 5.41, Collecting the Solid by Suction Filtration).

9. The amount varies, depending upon the completeness of the bromination.

10. 2-Bromo-4-nitrotoluene has a pale-yellow color and melts at 77.5°. Yield is 75 to 80%.

Questions

1. What is the minimum volume of water necessary to dissolve 0.3 mole of hydrogen bromide?

2. What is the function of the iron?

3. Why should the iron be in a finely divided form?

4. Which reagent is in excess, and why?

5. What impurities does the crude product contain, before being shaken with warm water?

6. What is the purpose of shaking it with hot water?

7. What is the purpose of the sodium bisulfite?

8. What is the purpose of washing with alcohol?

9. Is bromine attached to the benzene ring as reactive as bromine in alkyl bromides?

10. Which is most easily brominated: toluene or *p*-nitrotoluene? Discuss.

11. Would you expect much of the isomeric 3-bromo compound to be formed? Explain.

12. Do bond-energy values apply to a gaseous or liquid system?

13. For this particular system, is the actual ΔH different from the ΔH calculated from bond-energy values? Explain.

14. Explain why it is necessary to heat the reaction mixture.

15. Is there any objection to heating the mixture strongly?

16. What would be the market value of the hydrobromic acid obtained in this experiment if it were in the form of pure constant-boiling acid?

17. What are the probable impurities in the final product?

Experiment 30–3   Preparation of Benzyl Chloride
(*Caution:* Note 1)

Provide a dry 0.5-liter two-necked round-bottomed flask with a thermometer that reaches nearly to the bottom and with a dry chlorinating tube (see Figure 30–1 and Note 2). Make connections to the flask and chlorinating tube with tightly fitting and carefully bored cork stoppers (Note 3). Rubber cannot be used because the hot organic liquids soften and dissolve rubber. Insert into the reaction chamber through the side openings a thermometer and a chlorine-admitting glass tube, the latter extending nearly to the middle of the chamber, and drawn to an opening of 1 to 2 mm. To the top attach an efficient, dry reflux condenser (Note 4) and to this a glass exit tube which leads to a line of three 1-liter flat-bottom flasks containing, respectively, about 0.5 liter of water, 0.5 liter of aqueous sodium hydroxide, and 0.5 liter of alcoholic sodium hydroxide (or alcohol and 10 to 20 g. of flake caustic). Be sure that all connections are air-tight. Rubber stoppers may be used in the absorbing train. Keep the ends of the inlet tubes at all times well above the level of the liquids. With this absorbing train the experiment can be performed on the laboratory desk. Manipulation of the apparatus is easier here than in the hood.

Fig. 30–1   Chlorination Tube

The stream of chlorine from a cylinder (Note 5) should pass through a wash bottle of concentrated sulfuric acid before entering the reaction chamber, and the reaction chamber should be illuminated by an arc lamp (Note 6).

Place 1.0 mole of toluene and a few boiling chips in the 0.5-liter flask, and boil vigorously. As soon as the liquid refluxes freely from the condenser, illuminate the reaction chamber with an arc lamp, and turn on a slow stream of chlorine (Note 7). Then gradually increase the chlorine flow until the thermometer indicates a temperature of 130° to 140° in the reaction zone. *Caution:* Since an excess of chlorine may cause an explosion, *it is necessary that toluene be in excess at all times,* as shown by its refluxing from the condenser.

The progress of the reaction can be followed by watching the reading of the thermometer in the boiling liquid. As this approaches 165°, it may be necessary to cut down the chlorine flow. The reaction is essentially complete when the reading is 176° to 177° (Note 8).

Distil slowly without a column or else through a very short column, removing any toluene and dissolved hydrogen chloride at as low a temperature as possible. Collect a 5° fraction near the boiling point of benzyl chloride. Calculate the percentage yield (Note 9).

Notes

1. Use care in handling the product, for it is a lachrymator. Do not spill any of it on the desk or floor nor get it on the skin, especially on the face. Make all transfers in the hood. Save the alcoholic sodium hydroxide for washing out all the vessels (do all washings in the hood), and *pour all washings down the sink in the hood, not down the open laboratory sinks. Do not contaminate the laboratory.* In case any benzyl chloride is spilled on the skin, remove by washing with alcohol.

2. The reaction chamber should have a capacity of about 300 cc., and the lower vertical tube, 2.5 to 2.8 cm. diameter and about 25 cm. long, should be packed for 20 cm. with glass rings, 5 x 5 mm. (or other suitable packing). If the column has a tendency to flood, it may be desirable to wrap it with asbestos cord. Flooding is more likely if the diameter of the tube is less than 2.5 cm.

3. The cork stoppers must be carefully selected and bored, so as to be air-tight (Experiment 3-1, Note 4). However, the thermometer and chlorine tube may be attached by rubber tubing. Where rubber tubing is used in the absorbing train, in connecting glass tubing, the glass tubes should touch so that rubber is not exposed to chlorine, which causes rapid deterioration of rubber.

4. Preferably a short efficient condenser, such as a bulb or Friedrich's condenser. Take care that the refluxing liquid does not hit the thermometer.

5. It is not recommended that the chlorine be generated, because in general it is difficult to get a sufficiently rapid and well-regulated flow of gas. *Caution:* Do not let chlorine escape into the laboratory: *do not breathe it.*

6. Illumination by sunlight is satisfactory although usually not convenient.

7. Exercise caution, avoiding a sudden spurt of chlorine, which might carry sulfuric acid over. Since the valves on chlorine cylinders stick badly, they are hard to turn on gently. Take the cylinder to the hood, and open the valve by tapping the valve handle. Then close it. It should be easy to regulate after having been opened once.

8. About 1 hour is required.

9. Since the product is contaminated by comparatively small amounts of hydrogen chloride and toluene, *slow* distillation at first from a distilling flask removes these impurities satisfactorily. Usually there is little or no higher-boiling impurity. If an air condenser is used, the distillation then should be done in the hood. The yield is 80%.

Questions

1. What is the function of each of the three 1-liter flasks?
2. Why does an insoluble liquid appear in the first one of these?
3. Can the loss from this source be overcome? Explain.
4. Why should the inlet tubes be well above the surfaces of the liquids?
5. Why is illumination desirable?
6. What other reactions are possible?
7. Is there evidence that any other reactions took place?
8. How can a mixture of *o*- and *p*-chlorotoluenes be obtained from toluene?
9. Compare benzyl chloride, bromobenzene, and *n*-butyl chloride in the rapidity with which the halogen atom is replaced by the hydroxyl, amino, or other group.
10. Do bond-energy values apply to a gaseous or to a liquid system?
11. For this particular system is the actual ΔH much different from the one calculated from bond energies?
12. What experimental evidence indicates whether ΔH is positive or negative?
13. What are the probable impurities in the product?
14. Why should the refluxing liquid not hit the thermometer?

Experiment 30–4   Properties of Aromatic Halogen Compounds

Add one drop or one crystal (if a solid) of the following compounds, free of hydrogen halide, separately to 1 ml. of alcoholic silver nitrate: *n*-butyl bromide, bromobenzene, 2-bromo-4-nitrotoluene, benzyl chloride.

Questions

1. How may the compounds be freed of hydrogen halide?
2. How do you account for differences in rates of reaction with silver nitrate?
3. Is there any relationship between general reactivity of aromatic halogen compounds and the position of the halogen atom in the molecule?

Chapter 31

SULFONIC ACIDS

Aromatic sulfonic acids are obtained usually by direct sulfonation with: (a) sulfuric acid (slightly diluted, concentrated or 100% acid), (b) fuming sulfuric acid, or (c) chlorosulfonic acid:

(a) $\qquad CH_3C_6H_5 + HOSO_2OH \rightarrow p\text{-}CH_3C_6H_4SO_2OH + H_2O$

$\qquad\qquad BrC_6H_5 + HOSO_2OH \rightarrow p\text{-}BrC_6H_4SO_2OH + H_2O$

(b) $\qquad 1,4\text{-}CH_3C_6H_4NO_2 + SO_3 \rightarrow 1,2,4\text{-}CH_3C_6H_3(SO_2OH)NO_2$

(c) $\quad CH_3CONHC_6H_5 + 2HOSO_2Cl \rightarrow$

$$p\text{-}CH_3CONHC_6H_4SO_2Cl + H_2SO_4 + HCl$$
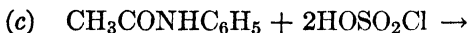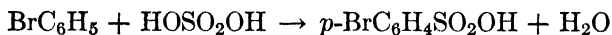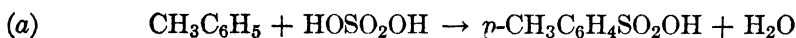
31.11 Thermochemistry. It is possible to calculate, from bond energies, values of ΔH for the gas-phase reactions a and c, namely, 5.0 and 3.3 kcal. respectively, but these are only rough approximations, since the effect of the ionic character due to formal charges and the stabilizing effect of resonance in sulfuric acid, chlorosulfonic acid, and the organic sulfonic acid are difficult to estimate. Since the heats of vaporization of these acids are not well known and probably are quite high, ΔH for the liquid phase is even less certain.

Experimentally, the sulfonation reaction with sulfuric acid alone is mildly exothermic, whereas with 30% fuming acid or with chlorosulfonic acid considerable heat is evolved. Consequently only with these last two is it necessary to take the usual precautions to be observed when keeping a reaction under control.

31.12 Rates. The rates of sulfonation increase in the order: Diluted sulfuric acid < concentrated sulfuric acid < 100% sulfuric acid < chlorosulfonic acid and fuming acid. The presence of water so decreases the rate that even phenols, the most easily sulfonated aromatic compounds, do not react with 75% sulfuric acid. On the other hand, the sulfonation reaction is markedly accelerated if sulfur trioxide is present.

The particular sulfonating agent to be employed and the temperature at which the reaction is to be carried out are determined by the nature

of the compound to be sulfonated, by the number of sulfonic groups to be introduced, and by the nature of the desired product, that is, whether a sulfonic acid or a sulfonyl chloride. Benzene is usually sulfonated by the use of a fuming acid of 5 to 10% sulfur trioxide. However, it may be sulfonated with concentrated acid by long heating, either using a large excess of acid or removing the water as it is formed as in the case of toluene sulfonic acid (Experiment 31–1). An *ortho–para*-directing radical (except halogen) attached to the benzene ring imparts greater reactivity and thus greater ease of sulfonation, whereas a *meta*-directing radical brings about lower reactivity. Thus toluene is slowly sulfonated by hot concentrated sulfuric acid, and mesitylene rapidly by warm acid. Likewise, bromobenzene can be sulfonated. However, in this case fuming acid (Experiment 31–3) or a long period of heating with concentrated acid is necessary. Nitrotoluene (Experiment 31–2) requires the use of 30% fuming acid and some heating.

In general, except for easily sulfonated compounds, fuming acid containing 5 to 30% anhydride is used. If the anhydride content is much above 30%, as for example 60%, charring is liable to take place and even may be quite extensive. A side reaction is the formation of a sulfone, which becomes more prominent with increase in anhydride content.

31.13   Isolation and Purification. The isolation of a sulfonic acid from a reaction mixture, which usually contains sulfuric acid, and the subsequent purification necessitate a procedure different from that used for volatile compounds. In those cases where the acid is insoluble, or only slightly soluble in water, dilution of the reaction mixture with water throws down the solid acid, which then can be filtered from the unreacted sulfuric acid. The sulfonic acids which can be so isolated are those of high molecular weight. Some acids which are soluble in water, for example *para*-toluene sulfonic acid, can be crystallized from concentrated hydrochloric acid solution.

Generally, water-soluble sulfonic acids are best recovered from their reaction mixtures in the form of salts. In some cases the sodium salt (Experiment 31–3), in others the potassium salt (Experiment 31–2), is best, depending on which is the less soluble. The solubility of a salt is decreased by the presence of a second salt having a common ion. Thus sodium sulfate decreases the solubility of sodium *p*-bromobenzene sulfonate (Experiment 31–3). The crude salt usually is contaminated with some of the inorganic salt. It may be purified by washing thoroughly with water before the mother liquor dries or, better, by crystallization from hot water or from a more suitable solvent, for example hot

alcohol. But, since the desired salt is liable to be very soluble in water, as many sodium sulfonates are, much loss may attend the purification from water, unless it is carried out with especial care.

A complete removal of sulfuric acid or of sulfate ion from a sulfonic acid usually can be accomplished by a more elaborate procedure involving the preparation of the barium or calcium salt. The mixture after dilution with much water is digested with barium or calcium carbonate or hydroxide (if the hydroxide is used, the excess base should be precipitated later by carbon dioxide) until all acid is neutralized, the precipitated barium or calcium sulfate and excess carbonate are removed by filtration, and the soluble barium or calcium sulfonate recovered by evaporation of the filtrate. In case the sulfonic acid itself is desired, metathesis of the barium or calcium salt in aqueous solution with the correct amount of sulfuric acid gives an insoluble sulfate and the soluble acid, which is recovered by filtration, and evaporation of the filtrate. In case the potassium salt is desired, potassium carbonate or sulfate is used in place of the sulfuric acid. Other salts can be prepared by the use of the proper carbonate or sulfate.

The formation of a sulfonchloride instead of the sulfonic acid by the use of chlorosulfonic acid is in many cases an advantage, since the sulfonchlorides are usually insoluble or only sparingly soluble in water, but soluble in ether and distillable at reduced pressure. Chlorosulfonic acid is hydrolyzed readily by cold water into sulfuric acid and hydrochloric acid, whereas organic sulfonchlorides react but slowly. Thus, pouring the reaction mixture onto ice to decompose the chlorosulfonic acid and adding ether or other suitable organic solvent extracts the product from inorganic contaminants. Sometimes the sulfonchloride is a solid, as in the preparation of sulfanilamide (Experiment 31–4) and can be recovered by filtration. Chlorosulfonic acid is especially useful when *ortho* and *para* isomers are to be separated, as for example *o*- and *p*-toluenesulfonyl chlorides. Fractional crystallization as well as fractional distillation can be used here, for the *para* isomer is a solid, whereas the *ortho* isomer is a liquid.

When the acid is wanted rather than the sulfonchloride, long refluxing of the pure sulfonchloride with water causes hydrolysis to the sulfonic acid and hydrochloric acid; evaporation to dryness, repeated if necessary, eliminates the latter and leaves a fairly pure sulfonic acid.

When a sulfonamide is wanted, as for example in identification, or in the preparation of sulfanilamide (Experiment 31–4), chlorosulfonic acid is especially valuable, since the organic sulfonchloride readily undergoes ammonolysis. The starting material is acetanilide rather than aniline,

since the amino group must be protected. The reactions subsequent to chlorosulfonation are shown below.

p-CH$_3$CONHC$_6$H$_4$SO$_2$Cl + 2NH$_3$ →

$$p\text{-CH}_3\text{CONHC}_6\text{H}_4\text{SO}_2\text{NH}_2 + \text{NH}_4\text{Cl}$$

p-CH$_3$CONHC$_6$H$_4$SO$_2$NH$_2$ + H$_3$O$^+$ →

$$p\text{-}\overset{+}{\text{N}}\text{H}_3\text{C}_6\text{H}_4\text{SO}_2\text{NH}_2 + \text{CH}_3\text{COOH}$$

$2p$-$\overset{+}{\text{N}}$H$_3$C$_6$H$_4$SO$_2$NH$_2$ + Na$_2$CO$_3$ →

$$2p\text{-NH}_2\text{C}_6\text{H}_4\text{SO}_2\text{NH}_2 + 2\text{Na}^+ + \text{H}_2\text{O} + \text{CO}_2$$
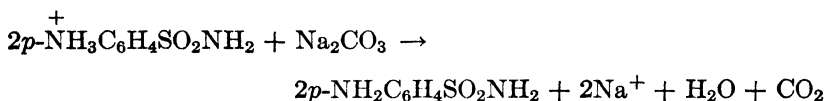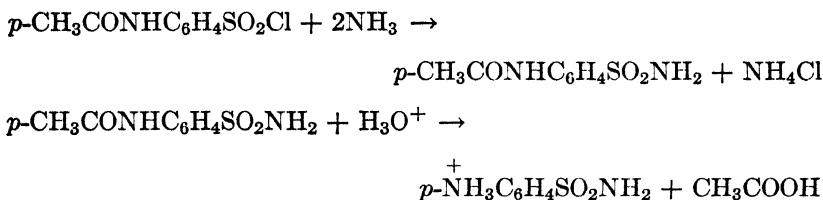
Sulfanilamide is the simplest example of a large number of sulfa drugs, all of which have the structure p-NH$_2$C$_6$H$_4$SO$_2$NHR. For the preparation of any of these, p-acetaminobenzenesulfonyl chloride p-CH$_3$CONHC$_6$H$_4$SO$_2$Cl reacts with a suitable amino compound. For example, sulfaguanidine (more correctly sulfanilylguanidine) is obtained by the action of p-acetaminobenzenesulfonyl chloride on guanidine. The sulfanilyl group p-NH$_2$C$_6$H$_4$SO$_2$—, is named from sulfanilic acid p-NH$_2$C$_6$H$_4$SO$_2$OH.

p-CH$_3$CONHC$_6$H$_4$SO$_2$Cl + 2H$_2$NC(=NH)NH$_2$ →

$$p\text{-CH}_3\text{CONHC}_6\text{H}_4\text{SO}_2\text{NHC}(=\text{NH})\text{NH}_2 + (\text{NH}_2)_2\text{C}(=\overset{+}{\text{N}}\text{H}_2)\overset{-}{\text{Cl}}$$

p-CH$_3$CONHC$_6$H$_4$SO$_2$NHC(=NH)NH$_2$ + H$_3$O$^+$ →

$$p\text{-}\overset{+}{\text{N}}\text{H}_3\text{C}_6\text{H}_4\text{SO}_2\text{NHC}(=\text{NH})\text{NH}_2 + \text{CH}_3\text{COOH}$$

$2p$-$\overset{+}{\text{N}}$H$_3$C$_6$H$_4$SO$_2$NHC(=NH)NH$_2$ + Na$_2$CO$_3$ →

$$2p\text{-NH}_2\text{C}_6\text{H}_4\text{SO}_2\text{NHC}(=\text{NH})\text{NH}_2 + 2\text{Na}^+ + \text{H}_2\text{O} + \text{CO}_2$$
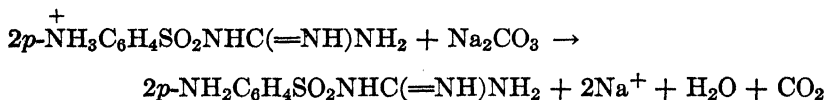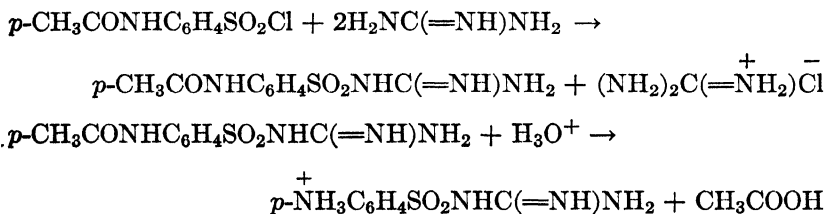
Experiment 31-1   Preparation of p-Toluenesulfonic Acid

Equip a three-necked flask with a sealed mechanical stirrer (Note 1) and an efficient fractionating column (Note 2), making connections with tightly fitting cork stoppers (Note 3). To the side arm of the fractionating tube attach a condenser which drains into a phase separator (Figure 21–1. Refer to Experiment 21–2 for additional details).

Place 4 moles of toluene and 2 moles of c.p., concentrated sulfuric acid in the flask (Notes 4 and 5). Heat to boiling while stirring con-

tinuously, and distil over an azeotropic mixture of toluene and water (Note 6). Collect the water, and note the volume (Note 7). After about 4 hours remove a small amount of the lower phase, and test for sulfate ion. Repeat on a sample of similar size at intervals of about 0.5 hour until the test is essentially negative, usually in about 6 hours (Note 8). Towards the last, divert the toluene from the reaction flask, until little remains. Be sure however that some is present. Otherwise, if the temperature rises too high, decomposition may take place. Take this recovered toluene into account in calculating the percentage yield.

While it is still molten (*Caution:* flames) pour the reaction mixture into a beaker. After it has cooled and solidified, let excess toluene drain. Dissolve about one half of the mass in the minimum (75 to 100 ml.) of concentrated hydrochloric acid, heating cautiously so as not to lose much hydrogen chloride (Hood; Note 9). Allow to cool slowly, and finally cool to 0°. Collect by suction filtration, removing as much mother liquor as possible. (Refer to Section 5.4.) Free the solid as completely as possible of hydrochloric acid by absorption. Use the filtrate for recrystallization of the second half of the solid, as before. Spread the solid in the air to permit evaporation of the hydrochloric acid. Calculate the percentage yield (Notes 10 and 11).

Notes

1. Refer to 15.17. If the stirrer is reasonably close to the bottom, no danger of decomposition is associated with flame heating.

2. The fractionating tube should provide sufficient height for the condenser and phase separator. To obtain the azeotropic mixture of water and toluene, 13.5% water and distilling at 84°, a packing of cut glass rings, 75 cm. in length and reflux condenser is recommended.

3. Refer to Experiment 3–1, Note 4. Rubber stoppers become badly swollen.

4. If the amounts of reactants are less, it is difficult to obtain the azeotropic mixture, especially after the first 2 hours, owing to the slowness with which water is formed. A larger amount probably reacts more smoothly. Note the initial volume. In case it drops markedly, owing to loss of toluene, add more toluene. (*Caution:* Refer to Experiment 14–2, Note 3.)

5. Metallic impurities may increase the oxidizing reaction of sulfuric acid

6. If the temperature rises much above that of the azeotropic mixture, water may not separate. When the rate of water formation drops, use the column as a reflux condenser until water accumulates, and then increase the flame slightly so as to distil slowly.

7. Somewhat less than the theoretical amount of water is formed, about 32 ml. The operation can be discontinued and recontinued as desired.

8. Crystallization and purification are hindered by sulfuric acid. The more completely this reacts, the easier the recovery.

9. Even though the mixture is dark in color, there is no insoluble material if the experiment has been properly carried out; thus, filtration is not necessary. Filtra-

tion of the hot acid solution can be done through asbestos, or through a sintered glass plate. Filter paper disintegrates.

10. The yield of *p*-toluenesulfonic acid monohydrate is about 50%. The loss is due mainly to the high solubility of *p*-toluenesulfonic acid in water.

11. A higher yield of product may be obtained by the following different procedure, but the purity is lower. After the liquid has been transferred warm to a beaker, stir in just enough water to form the monohydrate. This melts at 106° and is less soluble in toluene than the anhydrous form. Allow to crystallize, collect by suction filtration, and press out strongly, to get rid of any liquid. Since most of the sulfuric acid will remain, it is essential that the reaction be carried practically to completion. However, sulfone formation may become important.

Questions

1. What is the order of the ease of sulfonation of the compounds: benzene, toluene, and nitrobenzene?

2. Name two factors which indicate that the foregoing procedure is not satisfactory in the sulfonation of benzene.

3. How can evidence of the undesirable reaction of oxidation be detected easily?

4. How does the presence of sulfuric acid hinder purification?

5. Is the reaction of sulfonation markedly reversible?

6. Is the reaction of sulfonation strongly exothermic?

7. What evidence in regard to this comes from the experiment?

8. Why is concentrated hydrochloric acid used for purification instead of water?

9. What is the main impurity or impurities in the crude and final products?

10. What steps were taken to eliminate them?

Experiment 31-2   Preparation of Potassium *p*-Nitrotoluene-*o*-sulfonate

Into a small flask weigh enough fuming sulfuric acid containing 30% sulfuric anhydride to furnish 0.1 mole of the anhydride, and close the flask. Make all transfers in the hood (*Caution:* Note 1). Into a 100- (or 200-) ml. flask with a long neck (Note 2) place 0.10 mole of *p*-nitrotoluene and add about one third of the fuming acid. Mix the contents thoroughly. Heat should develop (Note 3). If it does not, heat the mixture to about 70°. If heat develops at the higher temperature, add the remainder of the acid in two or three portions. If the mixture does not warm spontaneously at the higher temperature, add all the acid. Maintain a temperature of 80° to 100° (Note 4) until a test portion of 3 or 4 drops, when added to *ca.* 1 ml. of cold water, gives a clear solution (Note 5). The sulfonation should be complete after about 1 hour (Note 6). In the meantime, dissolve in 100 ml. of water an amount of technical flake potassium hydroxide (Note 7) which is a 5 to 10% excess over the amount necessary to convert the excess sulfuric acid to

potassium bisulfate (Note 8) and the sulfonic acid to its potassium salt (see Question 4).

After the sulfonation is complete, cool the liquid, and pour it with stirring into 150 ml. of water in a beaker. Add with stirring the solution of potassium hydroxide (Note 9), and apply heat if any solid salt separates. Heat to boiling. Add 1 to 2 g. of decolorizing carbon, boil for several minutes, filter rapidly while hot, observing the usual precautions to avoid cooling. On standing, large crystals of the potassium salt separate. Remove these by suction filtration, and obtain a second crop by evaporation of the filtrate and washings to about one third of the original volume (Note 10; see Question 5). Dry the crude salt in the air (Note 11), and determine the percentage yield.

Recrystallize from the minimum quantity of boiling water (Note 12). If it is dark colored, add 1 or 2 g. of decolorizing carbon and boil for a few minutes (refer to Section 5.2). Determine yield of pure product (Note 13).

Notes

1. *Caution:* Use extreme care in working with this *very* corrosive liquid. Make all transfers in the hood. Do not let any of the acid drop on the desk, skin, or clothing. Avoid letting it run down the outside of vessels from which it is being poured. Set the vessels on a pad or block of inexpensive material. If any is spilled, at once dilute with water and neutralize with sodium bicarbonate solution.

2. A Kjeldahl flask is recommended, as the long neck facilitates handling and acts as a condenser.

3. Occasionally the fuming acid may be stronger than 30%. If so, considerable heat is developed on the addition of the first portion of the acid. Then it will be necessary to cool the mixture to about 50° before adding more acid.

4. Decomposition may take place if the temperature is too high. In case heating is done with a steam bath, protect against moisture.

5. Sufficient water must be present to dissolve the sulfonic acid.

6. Incompleteness of sulfonation by this time may be due to a low SO_3 content of the fuming acid. An additional small amount (5 g.) should be added.

7. Technical potassium hydroxide in flake form is about 90% pure, whereas the pure stick and pellet forms contain about 85% potassium hydroxide. The sticks and pellets have about 12% water and 3% potassium carbonate. The main impurities of the flake form are potassium carbonate 3%, and potassium chloride 1.5%. For neutralization purposes therefore, the flakes may be regarded as essentially 95% potassium hydroxide.

8. A small excess of base is taken to insure that no free sulfuric acid is present. Inspection of Figure 2–1 shows why conversion to potassium bisulfate is preferred to potassium sulfate. *Check calculations with instructor before proceeding.*

9. Sodium hydroxide is not satisfactory, for the sodium sulfonate is quite soluble.

10. The second crop is about 10% of the first crop.

11. Air drying is safer. The salt sometimes decomposes in an oven set at 100°, mainly because of local overheating.

12. The approximate solubility of potassium *p*-nitrotoluene-*o*-sulfonate in water, grams per 100 g., is: at 20° 3.35 g., at 35° 6.8 g., and at 50° 9.6 g. The solubility is much lower in potassium bisulfate solution.

13. The yield of crude product is 85 to 90%, and of recrystallized product 70 to 75%. When pure, the salt is pale yellow in color.

Questions

1. What is the order of the ease of sulfonation of the three compounds: benzene, toluene, and nitrotoluene?

2. Would you expect much of the *m*-sulfonic acid to be formed in this experiment? Explain.

3. Aside from the saving in cost, is there any advantage in converting sulfuric acid to potassium bisulfate, rather than to potassium sulfate? Explain.

4. What is the weight of potassium bisulfate that can be formed from the reaction mixture, if it is assumed that the optimum weight of pure potassium hydroxide is added?

5. To what volume may the filtrate from the first crop of crystals be evaporated without having any inorganic salt crystallize at room temperature? (Assume no potassium sulfate or sodium salts present.)

6. How do you account for the fact that the salt prepared in this experiment is less stable when heated than sodium *p*-bromobenzenesulfonate?

7. How may sulfonic acids be converted into sulfonyl chlorides? sulfonamides? phenols?

8. What are the probable impurities in the product?

Experiment 31-3   Preparation of Sodium
p-Bromobenzenesulfonate

Weigh 0.10 mole of bromobenzene into a 125-ml. conical flask, and into a small (50-ml.) conical flask weigh enough 30% fuming sulfuric acid (*Caution:* Note 1) to furnish 0.08 mole of sulfur trioxide. Add the acid to the bromobenzene slowly and with good agitation during the course of 5 to 10 minutes (Note 2). The small flask can be rinsed out at the last by some of the reaction mixture if desired. Heat the mixture to 120° for 5 minutes to complete the reaction (Note 3), and then cool. With vigorous stirring, pour the cold mixture into 50 ml. of water in a 200-ml. beaker (Note 4), and remove any insoluble precipitate by suction filtration.

Add gradually without cooling and with stirring until completely dissolved an amount of sodium hydroxide pellets which is a 5 to 10% excess over the amount necessary to convert the sulfonic acid to the sodium salt and the excess of sulfuric acid to sodium bisulfate (Note 5). Let stand overnight, or cool to approximately 10° (Note 6), and let stand at about 10° for about ½ hour, with occasional agitation.

Collect the sodium *p*-bromobenzenesulfonate by suction filtration on a funnel small enough to give a fairly thick layer of solid. Take special care to effect removal of dissolved impurities (Section 5.4). Wash once with 2 ml. of cold water, using a medicine dropper to apply the water to all parts of the solid. Remove to filter paper or porous plate for complete drying. Calculate the percentage yield of this crude product.

Purify the product by crystallizing from the minimum amount of hot 50% aqueous alcohol (refer to Experiment 5–1), filtering the hot solution if not clear, and cooling to 0° before collecting the solid. Wash once with *ca.* 10 ml. of cold 50% alcohol (Note 7). Calculate the percentage yield of the dry recrystallized product (Note 8).

Notes

1. *Caution:* Use extreme care in working with this *very* corrosive liquid. Make all transfers in the hood. Do not let any of the acid drop on the desk, skin, or clothing. Avoid letting it run down the outside of vessels from which it is being poured. Set the vessels on a pad or block of inexpensive material, not directly on any permanent desk or hood top. If any is spilled, dilute at once with water, and neutralize with sodium bicarbonate solution.

2. The side reaction is less extensive if the acid is poured into the bromobenzene. Although the sulfonation takes place within less than 1 minute if 0.1 mole of SO_3 is taken, sulfone formation is more important than with 0.08 mole.

3. A clear solution does not indicate complete sulfonation, because bromobenzene is somewhat soluble in the mixture of sulfuric and *p*-bromobenzenesulfonic acids.

4. The amount of water can be less and still keep the sodium bisulfate in solution. The mixture then is more difficult to handle. See Question 4. (Refer to Figure 2–1.) The solubilities of sodium and potassium *p*-bromobenzenesulfonates at 20° are 18.0 and 14.5 g., respectively, per 100 g. of water.

5. The solid does not dry well if any sulfuric acid remains. The amount of sodium sulfate should be kept to a minimum because the solubility in water becomes low at 10°. Moreover, it is much less soluble in 50% alcohol than is sodium bisulfate. Assume that the sodium hydroxide is 96% pure. *Check calculation with instructor before proceeding.*

6. If cooled further, sodium sulfate decahydrate may crystallize in case much is present.

7. The temperature coefficient of solubility of the salt is greater in 50% aqueous alcohol than it is in water. The solubility in the former solvent at 80° is *ca.* 45 g., and at 5° *ca.* 6 g. per 100 ml. of solvent.

8. The yield of crude product is 85 to 90%, and of purified product 70 to 75%.

Questions

1. Write the equation for the formation of the solid which precipitates when the reaction mixture is diluted with water.

2. Does it seem logical that more sulfone is produced when the bromobenzene is poured into the fuming acid? Explain.

3. Do you believe that bromobenzene is as soluble in concentrated sulfuric acid alone as it is in a mixture of concentrated sulfuric acid and *p*-bromobenzenesulfonic acid?

4. How much water is necessary to dissolve at 25° just the expected amount of sodium bisulfate without supersaturation, assuming no other salt is in solution and that all sulfuric acid is converted to sodium bisulfate?

5. Aside from the saving in cost, what is the advantage in converting sulfuric acid to sodium bisulfate rather than to sodium sulfate?

6. What effect do you expect dissolved sodium sulfate to have on the solubility of sodium *p*-bromobenzenesulfonate in water? Explain. Would potassium sulfate have any effect? Explain.

7. Which is more easily sulfonated: benzene or bromobenzene?

8. What are the probable impurities in the product?

Experiment 31–4   Preparation of Sulfanilamide

CHLOROSULFONATION. To about 0.4 mole of chlorosulfonic acid (*Caution: hood;* Note 1) in a suitable flask (*ca.* 125 ml.) and kept cold by an ice bath, add in small portions and with good mixing 0.10 mole of dry crystalline acetanilide (Note 2). Maintain the temperature at 10° to 20°. Let stand at 25° to 30° until the evolution of hydrogen chloride slackens. Cover with an inverted small beaker, and heat on a steam bath, taking care that evolution of hydrogen chloride is not too vigorous and that water or steam does not enter the flask. Agitate frequently. Heat until little or no hydrogen chloride is evolved on agitation. This will require at least 0.5 hour.

Cool to room temperature, and pour in a thin stream with agitation into enough *clean* crushed ice to reduce the concentration of sulfuric acid to about 25% (Note 3). Stir for a few minutes to aid crystallization, adding more ice if necessary to keep cold. Without delay (Note 4) collect the solid on a Buechner funnel, wash once or twice with small amounts of cold water, and convert the wet solid to the sulfonamide.

AMMONOLYSIS. Transfer the still moist *p*-acetaminobenzenesulfonchloride to the original reaction flask, and add 20 to 25 ml. of water, so as to have a workable paste. Add in portions with agitation enough concentrated ammonium hydroxide (*hood*) to furnish 0.4 to 0.5 mole of ammonia, mix thoroughly, and cool moderately if the mixture becomes hot. Mix the mass for several minutes with a swirling motion. If lumps are visible at this point, close the flask with a tightly fitting stopper, and shake vigorously until the paste looks smooth. Then with a small flame gradually increase the temperature to boiling, and boil until much of the excess ammonia has been driven out, agitating constantly (Note 5) to prevent bumping. Cool, collect the solid on a Buechner

funnel, and wash the solid once or twice with small amounts of cold water. The solid may be converted at once to sulfanilamide.

HYDROLYSIS. To the still moist p-acetaminobenzenesulfonamide in the original flask add enough C.P. concentrated hydrochloric acid to furnish 0.1 mole of hydrogen chloride and enough water to bring the concentration to ca. 3 N. Slowly bring to boiling with a small flame. To minimize bumping agitate constantly as long as a solid is present. Avoid local overheating; otherwise, darkening is promoted. Continue boiling gently for ca. 20 minutes, or until the reaction is complete (Notes 6 and 7). In case the solution is colored, heat for a few minutes with decolorizing carbon, and filter hot through a small fluted filter, preferably into a 100-ml. beaker. Wash the residue with a small amount of hot water. The total volume should be ca. 30 to 40 ml.

Weigh out enough solid sodium bicarbonate to furnish a slight excess over the hydrochloric acid added, and add it in small portions to the warm liquid (ca. 50°) with stirring until no more gas is evolved. Heat to 70° or 80° to dissolve the solid. The solution should be basic to litmus. Add concentrated hydrochloric acid to the hot solution, drop by drop, until it is neutral to litmus (Note 8). Sulfanilamide crystallizes on cooling. Collect on a small Buechner or Hirsch funnel, wash with very small amounts of cold water until free of chloride ion, dry, take the melting point, and calculate the percentage yield (Notes 9 and 10).

Notes

1. *Caution:* Chlorosulfonic acid is a highly corrosive liquid. Do not breathe the vapor, and do not spill it on the skin, clothes, desk, or floor. Immediately add aqueous ammonia to any spilled. Perform weighings and operation in the hood. See discussion regarding sulfonations with chlorosulfonic acid.

2. Chlorosulfonic acid reacts *very* rapidly with water with evolution of hydrogen chloride.

3. The solid separates better when the sulfuric acid concentration is not over 30%.

4. The organic sulfonchloride reacts slowly with water. In the finely divided state it reacts reasonably rapidly with ammonia.

5. Heating for about 20 minutes usually is sufficient. The excess of ammonia should not be large; otherwise, some of the organic compound may dissolve.

6. Acetaminobenzenesulfonamide was first prepared by Gelmo in 1908. He noted a marked difference in the rate of hydrolysis of the two amide groups, especially in moderately dilute hydrochloric acid. However, in hot sulfuric acid (density = 1.80) or in hot caustic solution (1:1) the molecule is cleaved to sulfanilic acid, acetic acid, and ammonia. In the experiment as performed there is some excess of hydrochloric acid, since the yields are not quantitative up to this point. However, hydrolysis of the sulfonamide group is not extensive during the comparatively short time of heating, because of the relatively low acid concentration.

7. The amounts of the sulfanilamide and its hydrochloride which are present are soluble in the specified amount of water at 80° to 90°. The solubility of sulfanilamide in water at 15° is 0.4 g. per 100 g.

8. Remove a small drop on a stirring rod to neutral litmus paper. The virtual cessation of gas evolution is an added indication. Sulfanilamide is both a weak acid, $K_a = 10^{-11}$, and a weak base, $K_b = 10^{-10}$.

9. Pure sulfanilamide melts at 163°. The yield is 55%. Recrystallize from the minimum of hot water, as before, if colored, or if the melting point is low.

10. Sulfanilamide should not be used as a medicine except on the advice of a physician. Sulfa drugs in general have been observed to affect the kidneys adversely when taken as medicines. Many also cause a pronounced diminution in the number of white corpuscles in the blood.

Questions

1. How is chlorosulfonic acid made?

2. To what class of compounds (besides being an acid) does it belong?

3. What are the hydrolysis products of chlorosulfonic acid?

4. What are the hydrolysis products of the organic sulfonchloride?

5. Do acetaminobenzenesulfonamide and cold aqueous ammonia react? Explain.

6. What do you think would be formed if a cold dilute aqueous solution of sodium hydroxide were added to p-acetaminobenzenesulfonamide?

7. What would happen if they were heated together?

8. What amide groups are present in the molecule of p-acetaminobenzenesulfonamide?

9. Which of these is the more easily hydrolyzed?

10. Assuming that the yield of the acetaminosulfonamide is 70%, what is the approximate concentration of hydrochloric acid after this is converted to sulfanilamide?

11. Why not make sulfanilamide by the action of sulfanilyl chloride on ammonia?

12. Explain how the solution can become alkaline merely by adding an excess of sodium bicarbonate to the hot solution.

13. Why should the final solution not be acidic or basic?

14. Name two important reasons for the relatively low yield.

15. What are the probable impurities in the product?

16. What steps have been taken to remove them?

Experiment 31–5   Properties of Sulfonic Acids

A   Relative Strengths of Acids.   Dissolve about 0.001 mole of p-toluenesulfonic acid in about 10 ml. of water. Add one drop of phenolphthalein indicator, and add dilute base dropwise to phenolphthalein end point. Just discharge this color by dropwise addition of approximately 0.1 N hydrochloric acid. Add one drop of methyl orange indicator, and continue titration to a methyl orange end point. Repeat with about 0.001 mole of acetic acid, instead of toluenesulfonic acid.

B   Sulfonamide.   (Hood) In a loosely stoppered test tube heat 1 g. of benzenesulfonic acid (or 1 g. of p-toluenesulfonic acid, potassium p-nitrotoluene-o-sulfonate or sodium p-bromobenzenesulfonate) with 2 g.

of phosphorus pentachloride in an oil bath at 140° to 150° for about
½ hour. Allow to cool. Add dry benzene (*ca.* 5 ml.), heat to 40° or
50° by means of a warm water bath (*Caution* against fire), stir well for
a few minutes, and filter if a clear solution cannot be decanted. Add
10 ml. of concentrated aqueous ammonia, and agitate thoroughly until
all sulfonchloride has reacted. Recover the sulfonamide by allowing
the benzene to evaporate, and purify by crystallization from alcohol.
Some sulfonamides precipitate when the ammonia is added. Deter-
mine the melting point of the purified sulfonamide (Note 1).

Notes

1. Melting points of sulfonamides are: benzenesulfonamide 236–9°; *p*-toluene-
sulfonamide 137°; *p*-bromobenzenesulfonamide 160–1°; 2-methyl-5-nitrobenzene
sulfonamide 186°.

Questions

1. Explain different results in A.
2. Write equations for the reactions in B.
3. State the value of this type of reaction from an analytical point of view.
4. How may sodium *p*-bromobenzenesulfonate be converted into *p*-bromoben ·
zenesulfonic acid?
5. Compare the ease of sulfonation of benzene, toluene, and *p*-nitrotoluene.
6. For the sulfonation of benzene, fuming acid of 8 to 10% SO_3 is used. Cal-
culate the amount of 30% fuming and 96% H_2SO_4 that must be taken to make 100
g. of 10% fuming acid.
7. How much greater is the value of ΔH for the sulfonation of toluene with sulfur
trioxide than with sulfuric acid, as calculated from heat of formation data?

Chapter 32

AROMATIC NITRO COMPOUNDS

Aromatic nitro compounds usually are prepared by direct nitration with (a) dilute, concentrated, or fuming (95 to 100%) nitric acid; (b) a mixture of nitric and sulfuric acids; (c) anhydrous nitric acid in glacial acetic acid;

$$C_6H_6 + HONO_2 \rightarrow C_6H_5NO_2 + H_2O$$
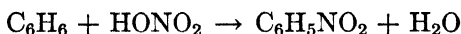
32.11 Thermochemistry. Calculation of $-\Delta H$ for the gas-phase nitration from bond energies (neglecting resonance energies) gives a value of 37.5 kcal., and for the liquid-phase nitration from heats of formation a value of approximately 36 kcal., if the heat of dilution of nitric acid by water is neglected. Actually, nitration in the liquid phase is strongly exothermic. On this account nitrations must always be carried out under proper control (Chapter 1).

32.12 Rates. The rate of nitration depends on the character of the aromatic compound and on the nitrating agent. For the latter the rates increase in the order: Dilute nitric acid < concentrated nitric acid < anhydrous (yellow fuming) nitric acid < concentrated nitric and concentrated sulfuric acids < fuming nitric and concentrated sulfuric acids < fuming nitric and fuming sulfuric acids. Little sulfonation is observed in the mixtures containing sulfuric acid, for the nitration reaction proceeds much more rapidly than sulfonation. Also, in many cases the sulfonic acid radical is replaced by the nitro radical. In general, red fuming nitric acid is little used, for the dissolved oxides of nitrogen often cause undesired reactions, such as oxidation.

The selection of the nitrating agent depends on the ease with which the compound reacts. In the case of benzene, nitration proceeds satisfactorily at 50° with a mixture of the concentrated acids (Experiment 32–1). Less active reagents may be used to nitrate compounds that have reactive positions due to the presence of an *ortho–para*-directing group, as for example alkylated benzenes, acylated amines, aromatic ethers, phenols, and naphthalene (however, aryl halides react more slowly than benzene). Two or three such groups in the *meta* position reinforce each other and render nitration easier. Thus the ease of nitration is in the order: Mesitylene > *m*-xylene ⊁ toluene > benzene.

The hydroxyl group has the greatest activating influence. Thus phenol is converted into a mixture of o- and p-nitrophenol by a diluted nitric acid, about 40%. For many nitrations with anhydrous nitric acid, glacial acetic acid is a satisfactory solvent, for it will dissolve the organic compound as well as the nitrating agent, as in Experiment 32-2, The Preparation of α-Nitronaphthalene.

Nitration is more difficult when a *meta*-directing group is attached to the benzene ring. Thus carboxylic acids, aldehydes, ketones, sulfonic acids, amine salts, and nitro compounds require a more powerful nitrating reagent than does benzene. An excellent reagent for obtaining *m*-dinitrobenzene from nitrobenzene is a mixture of fuming nitric and concentrated sulfuric acids. On the other hand, *p*-nitrotoluene can be nitrated to 2,4-dinitrotoluene by heating with concentrated nitric acid in a large excess of sulfuric acid. Trinitrotoluene can be obtained similarly, except that the reactivity of the mixture must be increased, either by using fuming nitric acid or by raising the temperature. These facts show the activating influence of the methyl group.

32.13 Effects of Sulfuric Acid. The beneficial effects of sulfuric acid in the reaction mixture are: (1) an increase in the rate of nitration, (2) better utilization of the nitric acid, and (3) inhibition of oxidation by nitric acid. The effect on the rate appears to be in part catalytic and in part an increase in the activity of the nitric acid. Thus, to convert benzene to nitrobenzene only a small excess of fuming nitric acid need be taken when sulfuric acid is present (about 1 mole), whereas in the absence of sulfuric acid a large excess of nitric acid, even if it is fuming, is needed. Indeed for this reaction only a slight excess of concentrated nitric acid is needed, if the amount of sulfuric acid is increased to 2 or 3 moles (Experiment 32-1). It is more economical to conserve nitric acid by the use of sulfuric acid, since the latter is much the cheaper.

Oxidation of amines and phenols by nitric acid may become quite pronounced, especially since the reaction is promoted by the products of reduction of the acid, namely, oxides of nitrogen and nitrous acid. Generally the oxidation becomes more extensive as the reaction proceeds. If the oxidation reaction is not prominent, it can be inhibited entirely by adding a small amount of urea, as in Experiment 32-1. This reacts with oxides of nitrogen and leads to a lighter-colored product. It is interesting that, when naphthalene is nitrated with fuming nitric acid in glacial acetic acid (Experiment 32-2), the addition of urea markedly hinders the nitration.

Sulfuric acid protects amines and phenols against oxidation. This probably is due mainly to salt formation. Sulfuric acid, because of its high proton activity, converts these much more completely into salts

than does nitric acid.   This greatly decreases the concentration of the free base, which is much more readily oxidized than the salt.   Acetylation is another method of protecting amines and phenols against oxidation.

32.14   Isolation and Recovery.   Introduction of a nitro group raises the boiling point markedly (benzene 80°, nitrobenzene 210°). Therefore, the desired product, if volatile, is easily separated from the original compound and from any dinitro compound.   The inorganic acids can be removed completely by washing with water and with aqueous bases.   Since nitro compounds decompose slightly when heated, and since the stability decreases with increase in the number of nitro groups, it is evident that only mononitro compounds can be distilled safely. Care should be taken that there is little or no dinitro compound in a mononitro compound that is being distilled.   Likewise, no nitric acid should be left in the product; otherwise, as distillation proceeds, further nitration may take place.

Many nitro compounds that boil too high to be distilled (nitronaphthalene, Experiment 32–2, dinitro compounds, etc.) are solids, and can be purified by crystallization.

Experiment 32–1   Preparation of Nitrobenzene
(*Caution:* Notes 1 and 2)

To an amount of concentrated nitric acid (sp. gr. 1.42; Note 3), sufficient to furnish a 10% excess of hydrogen nitrate over that required for the nitration of 0.70 mole of benzene, add gradually, with thorough mixing and cooling, twice its volume of concentrated sulfuric acid (sp. gr. 1.84; Note 4).   While the mixture is cooling, attach to a 500-ml. flask an air condenser (Note 5) and a thermometer that reaches nearly to the bottom of the flask (Note 6).   Place in the flask 0.70 g. mole of benzene.

With the benzene at 50° to 60° (Note 7), add 5 or 6 ml. of the nitrating mixture.   Shake *thoroughly* and *essentially continuously* (Note 8) as long as heat is evolved, and cool moderately if the temperature rises above 65°.   When the acid has largely reacted, as shown by a falling temperature on shaking, add a second portion of the acid, as before, with the temperature at 50° to 60°.   Later add larger portions.   The time for the addition of the acid should be 15 to 20 minutes.   After all the acid is added, shake continuously as long as the heat of the reaction keeps the temperature at 50° to 60°.   Immerse the flask in water at 60° to 70°, and shake *frequently*.   Continue until a test portion of a

few drops, when added to saturated salt solution (Note 9), has about the same density.

Cool the reaction mixture thoroughly, and in a large separatory funnel draw off the heavier acid layer (Note 10). Shake the nitrobenzene three or four times with water and then with aqueous sodium carbonate until the nitrobenzene is neutral to moist litmus paper (Notes 11 and 12). After separating from water, agitate the nitrobenzene, preferably in a small dry flask, with a few pieces of anhydrous calcium chloride. After it becomes clear, filter into a small distilling flask, and slowly distil off unchanged benzene and any water through a water-cooled condenser, which is replaced by an air-cooled condenser when the distilling temperature goes above 150°. Collect separately the portion which distils within a 5° range near the boiling point of nitrobenzene. Calculate the percentage yield (Note 13).

Determine the melting point of the product, and calculate the purity (refer to Table 4–1).

Notes

1. *Caution:* Nitrobenzene is a poison. Do not allow it to remain in contact with the skin, and take care not to inhale much of the vapor. Pour residues down the hood sink into a good stream of water. In case any of the concentrated acids is spilled on hands, clothing, or desks, at once add water, and neutralize with plenty of sodium bicarbonate solution.

2. This general procedure serves for the nitration of toluene and other aromatic hydrocarbons. In some cases (toluene) the amount of sulfuric acid can be decreased. For large-scale preparations, mechanical stirring is desirable.

3. The specific gravity of the acid should be taken, unless the concentration is known beyond any doubt. Even though the nitric acid is somewhat less concentrated, it may be used. Since this involves taking more water also, it may be necessary to increase the amount of sulfuric acid. Show calculations in your notebook, and consult the instructor.

4. If the temperature of the mixture is allowed to rise much above 60°, decomposition of the nitric acid may take place, as shown by the darker color and the evolution of oxides of nitrogen. The addition of 1 or 2 g. of urea to the nitrating mixture is desirable (see discussion).

5. Refer to Subsection 7.21 in regard to air condensers. A long-necked flask, for example a Kjeldahl flask, serves fairly well, instead of a flask with the air condenser, but some benzene may be lost.

6. The thermometer may be omitted if the worker is able to estimate temperature by touch.

7. If the temperature is much below 50°, the rate of reaction is quite slow; if above 65°, some dinitro compound may be formed. Also, nitric acid decomposes slowly near 65°, and benzene has a fairly high vapor pressure at 65°.

8. Agitation may be mechanical. However, sometimes a bad emulsion results, owing to fine air bubbles, if stirring is too vigorous. Also, the temperature cannot be controlled so readily.

9. A saturated aqueous solution of sodium chloride has a specific gravity of 1.1972

10. The spent acid, which contains a small amount of dissolved nitrobenzene, should be diluted with three or four volumes of water before it is poured down the drain. The recovery of the small amount of nitrobenzene that separates at this point is hardly worth the trouble involved.

11. Refer to Subsection 6.16 in case a troublesome emulsion develops.

12. When nitrobenzene containing nitric acid is distilled, decomposition may take place towards the end of the distillation. Sometimes the decomposition is quite sudden.

13. Usual yield is 85 to 90%.

Questions

1. What is the purpose of adding urea (Note 4)? Write the equation.

2. Why not reverse the order of addition when mixing benzene with the acid?

3. What purpose does the air condenser serve?

4. Why is vigorous shaking desirable?

5. To what extent must the reaction proceed before the organic liquid will sink when added to a large volume of water? half-saturated salt solution?

6. Is the presence of the sulfuric acid desirable? Explain.

7. Why should the reaction temperature be higher at the end than at the beginning?

8. How else could the nitration be effected?

9. How could dinitrobenzene be prepared?

10. From an industrial point of view, which reagent should be in excess?

11. Compare current prices of concentrated nitric and sulfuric acids.

12. Do you think the nitration of benzene by means of a mixture of concentrated nitric and sulfuric acids could be carried out at room temperature? Explain.

13. What is the principal impurity or impurities in the crude and final product?

14. What are the steps taken to remove them?

Experiment 32–2   Preparation of α-Nitronaphthalene

Dissolve 0.25 mole of naphthalene in 50 ml. of glacial acetic acid by heating to about 55° in a flask of suitable size (200 ml.). *Shake continuously,* preferably by a continuous swirling motion while cooling the flask either in a pan of water or under the tap, so as to obtain a *loose mass* of *finely* divided crystals (Note 1). Dilute enough fuming nitric acid (sp. gr. 1.50; Notes 2 and 3) to furnish an excess (Note 4) by pouring it, chilled, into 25 ml. of chilled glacial acetic acid, with cooling in an ice bath (Notes 5 and 6). Add this chilled acid gradually in several portions, with thorough mixing, to the naphthalene solution. Keep the temperature of the reaction mixture between 15° and 25° while the acid is being added. After all of the nitration mixture has been added, remove the flask from the bath, and allow the temperature to rise spontaneously to 40°, but not higher. The naphthalene, if properly crystal-

lized, will disappear within 3 to 5 minutes. Keep the temperature at 35° to 40° for 2 hours. At first some cooling may be necessary. Later, insulation by wrapping in a towel will keep the flask warm. Let stand for 24 hours.

A mass of crystalline nitronaphthalene should have formed. If no solid is present, add one or two seed crystals or induce crystallization by scratching the inside of the flask gently with a glass rod. Since the aim is to obtain large crystals, do not agitate, or start a large number of fine crystals. Let stand another 24 hours. By this time the nitronaphthalene should have crystallized as a mass of interlacing needles. If the crystallization is rapid, the solid comes out as a mass of finely divided crystals. Break up the crystal mass, and collect the solid by suction filtration (Notes 7 and 8), taking care to avoid contamination of the filtrate, especially by water from the aspirator. Save both the filtrate and the solid. Spread the solid on paper or porous tile, and remove as much of the solvent as possible by absorption. Let stand in the air until the acetic acid has evaporated. Determine the weight and melting point of this crop.

Return the filtrate to the original flask where it will be seeded by some remaining crystals. Cool this mixture slowly by securely fastening it above crushed ice (not immersed), taking care that oil does not form (Note 9). After the mixture has been brought to approximately 0° during about 0.5 to 1 hour, allow it to stand for about 15 minutes. Break up the crystal mass. Allow to stand cold until crystallization seems to be complete. Collect the solid by suction filtration without allowing the temperature to rise. Dry as before. Calculate the yield of material which melts at 55° or higher (Notes 10 and 11).

Notes

1. The reaction proceeds better this way than if the naphthalene separates as large crystals or as a firm crystal mass. It should not stick to the glass but should be loose. If the operation is not done properly, redissolve, and recool.

2. *Caution:* Use extreme care. Fuming nitric acid is very corrosive. Immediately wash up and neutralize with sodium bicarbonate any which is spilled.

3. Determine the specific gravity of the acid unless it has been measured *recently.* If the strength is not less than 80 or 85%, it can be used. See tables for relation between specific gravity and composition.

4. The reaction is a bit slow, and yields are lower if excess is below 25%. The yield usually is 70% with either a 30 or 40% excess of nitric acid. If the excess is more than 50%, the product is less pure, owing probably to the formation of some dinitronaphthalene. From an economy point of view the excess should not be greater than 40%.

5. Considerable heat develops when fuming nitric acid is diluted with acetic acid. Better temperature control of the reaction results if the dilution is done beforehand. Since anhydrous nitric acid begins to decompose spontaneously at about 60° and decomposes fairly rapidly at higher temperatures, cooling is desirable during the dilution.

6. If the amount of solvent is larger, the loss of product is greater, for α-nitronaphthalene is somewhat soluble in glacial acetic acid at 0°. If the amount is smaller, the filtrations are more troublesome. Some of the dissolved nitration product in the filtrate from the second crystallization may be recovered by the procedure of Note 11. The conditions of the experiment are so controlled that fairly pure nitronaphthalene is obtained directly. The product is much purer than that obtained by a two-phase nitration with dilute nitric acid.

7. The funnel should not be too large. A 6-cm. Buechner funnel is good (refer to Section 5.4).

8. During the filtration take care not to breathe the vapor of acetic acid or get the nitronaphthalene solution on the hands. It produces a perdurable stain. Some of the stain can be removed if the hands are washed at once in alcohol.

9. The cooling must be done slowly because of the large temperature coefficient of solubility. If the cooling is too fast, the product separates as an impure oil. By the method described, solid forms at the bottom, and the crystals grow slowly if the mixture is not shaken.

10. The first crop should be quite pure, melting at 57–58°; the second slightly less so, 55–57°. Both are pure enough. A melting-point lowering of 0.4° corresponds to contamination by about 1% of naphthalene or 2% of dinitronaphthalene.

11. A third crop may be obtained from the filtrate by a technique that is useful in overcoming the tendency to separate as an oil. Cool in the original flask to approximately 0° by an ice bath. Measure into a graduated cylinder 5 or 6 ml. of water. Add 0.1 to 0.2 ml. of water to the acetic acid solution by means of a dropper. Agitate frequently at 0° until the fine emulsion produced by the addition of water becomes crystalline. If this change is slow, it may be necessary to add a small pinch of α-nitronaphthalene powder for seeding purposes. Now add about 0.5 ml. of water, and shake until this is crystalline. Continue until 5 or 6 ml. of water has been added. Filter cold. This crop adds about 15% to the yield but is less pure (m.p. usually 50–55°).

When 40% excess nitric acid is taken, this crop is so much smaller, about 5%, that its recovery is hardly worth while. However, by the addition of 25 ml. of concentrated sulfuric acid to the second filtrate followed by heating, dinitronaphthalene can be obtained. This is a mixture of the 1,5- and 1,8-isomers.

Questions

1. Which is more easily nitrated: benzene or naphthalene?

2. Would the result be as satisfactory if the reactants were added in the reverse order?

3. What would be the effect of having sulfuric acid present in the reaction mixture?

4. Why not add all the nitric acid, at 0°, at once, to all of the naphthalene?

5. Why not cool the reaction mixture to 0° before doing any filtering?

6. Why is oil formation undesirable?

7. What are the main contaminants of the first and second crops?

8. Why does the product always separate as an oil and not as crystals on the addition of water to the filtrate from the second filtration?

9. How may β-nitronaphthalene be obtained?

10. How many dinitronaphthalenes are possible?

11. What other nitrating agent is sometimes used to prepare α-nitronaphthalene from naphthalene?

12. What are possible impurities of the product? What steps have been taken to remove them?

Experiment 32–3   Properties of Nitro Compounds

A SOLUBILITY. Test the solubility of nitrobenzene in sulfuric acid by adding about 1 ml. to 4 or 5 ml. of the concentrated acid. In case one phase results, add the solution to about 10 ml. of water.

B REDUCTION TO PHENYLHYDROXYLAMINE. Add to 10 ml. of water in a small flask 0.2 g. each of nitrobenzene and of zinc dust and 0.5 g. of ammonium nitrate. Shake vigorously for several minutes. Add 1 or 2 drops of the clear solution (filter if necessary) to a few milliliters of Tollen's reagent (Experiment 25–5, Note 3) or ammoniacal silver nitrate. A precipitate of metallic silver is due to the presence of phenyl-hydroxylamine. If the reaction is negative, repeat the reduction, with heating (Note 1).

C REDUCTION EQUIVALENT OF NITROBENZENE. Weigh about 1 g. (±0.01 g.) of nitrobenzene and 5 g. (±0.01 g.) of c.p. granulated tin (Note 2) in a small conical flask (Note 3). Add small portions of c.p. concentrated hydrochloric acid until 10 ml. have been added (Note 4), keeping the mixture warm, but not allowing it to get so hot that nitro-benzene distils out. Hydrogen should not be evolved. If it is, the re-agents are impure (Note 5). Finally heat, and agitate until all the nitro compound has reacted. Wash the residual tin once with cold 6 N hydrochloric acid, several times with water, and once with alcohol, and dry. Weigh to nearest 10 mg. Compare the theoretical quantity of tin required for reduction of the nitrobenzene with that actually dissolved (Note 6).

Notes

1. This is a general method of testing for the nitro group.

2. The tin works well if it is 10 to 20 mesh. If it is too fine, some may be dissolved by the acid. If it is too coarse, complete reduction of the nitro compound is difficult.

3. Good contact among the three phases is necessary. This is easier in a flask than in a test tube.

4. In case the first portion of the acid does not react, heat to about 60° before adding more. A high concentration of acid is undesirable (see 33.16).

5. Traces of metallic impurities in either the tin or the acid may act as catalysts, with the result that hydrogen is evolved.

6. Most nitro compounds are reduced quantitatively to the amine by tin and hydrochloric acid.

Questions

1. Write equations for the reactions in A, B, and C.

2. Was the dissolving in concentrated sulfuric acid due to a chemical change? Explain.

3. What is the function of ammonium nitrate?

4. What are the reduction products of nitrobenzene in an alkaline medium?

5. What is the reduction product of nitrobenzene in an acid medium?

6. What are the evidences of a chemical change with tin and hydrochloric acid?

7. Calculate ΔH for a liquid-phase nitration from data on heats of formation and heats of combustion.

8. How does heat of dilution with water affect this value?

Chapter 33

PRIMARY AROMATIC AMINES

Primary aromatic amines having the amino group on a side chain are prepared by methods used for aliphatic amines (Chapter 26). Nuclear primary amino groups are introduced mainly by (a) the Hofmann degradation of amides and (b) the reduction of nitro compounds:

(a) $C_6H_5CONH_2 + Br_2 + NaOH \rightarrow C_6H_5CONHBr + NaBr + H_2O$

$C_6H_5CONHBr + 3NaOH \rightarrow$

$$C_6H_5NH_2 + Na_2CO_3 + NaBr + H_2O$$

$$C_6H_4\begin{array}{c} CO \\ \diagup \quad \diagdown \\ \quad \quad \quad NH + Br_2 + 4NaOH \rightarrow \\ \diagdown \quad \diagup \\ CO \end{array}$$

$$1,2\text{-}NH_2C_6H_4COOH + Na_2CO_3 + 2NaBr + H_2O$$

(b) $\qquad C_6H_5NO_2 + 3H_2 \rightarrow C_6H_5NH_2 + 2H_2O$

$C_6H_5NO_2 + 3(NH_4)_2S \rightarrow C_6H_5NH_2 + 3S + 2H_2O + 6NH_3$

$C_6H_5NO_2 + 3Sn + 7HCl \rightarrow C_6H_5NH_3Cl + 3SnCl_2 + 2H_2O$

$C_6H_5NO_2 + 3SnCl_2 + 7HCl \rightarrow C_6H_5NH_3Cl + 3SnCl_4 + 2H_2O$

$HOC_6H_4NO_2 + 3Na_2S_2O_4 + 4H_2O \rightarrow HOC_6H_4NH_2 + 6NaHSO_3$
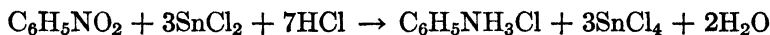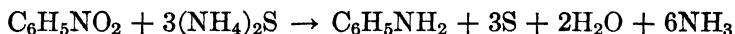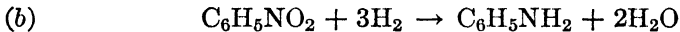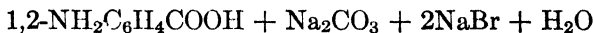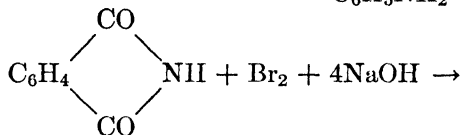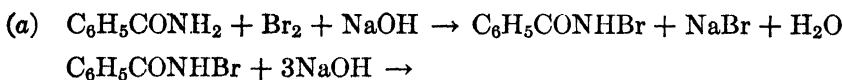
33.11 The Hofmann Degradation. Method a, which is discussed in detail under 26.15, often is employed when reduction methods b are not applicable, as when side reactions, such as reduction of the wrong group, accompany or precede the desired reaction. The degradation method is especially useful in converting phthalic acid or its derivatives, through the imide, to o-aminobenzoic acid or its derivatives.

33.12 Reduction of Aromatic Nitro Compounds. Method b is the usual method of preparing primary amines and may be carried out with a variety of reducing agents, as hydrogen, hydrogen sulfide, metals (iron, zinc, tin), or sodium hydrosulfite. The most commonly used reducing agent in beginning organic chemistry consists of tin and hydrochloric acid, as in Experiment 33–1, The Preparation of Aniline.

33.13 Thermochemistry. As noted under 26.13, the gas-phase hydrogenation of nitro compounds is very strongly exothermic (200

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kcal.). Reduction under acid conditions with an active metal such as
zinc, iron, or tin is even more strongly exothermic, since a strong acid
reacts exothermically with these metals to give hydrogen and exother-
mically with the amines to give salts. Reduction with sodium hydro-
sulfite is strongly exothermic also. The gas-phase reduction with hy-
drogen sulfide is more exothermic than reduction with hydrogen since
ΔH of formation of hydrogen sulfide is positive. In general, control is
necessary when reducing nitro compounds, because of the highly exo-
thermic nature of the reaction.

33.14 Rates. In general, even in a homogeneous system reduction
does not proceed rapidly at room temperature. Heating to about 50°
especially if the system is heterogeneous usually is desirable. Rates
often can be increased by adding alcohol to increase the solubility of
the nitro compound. Homogeneous systems may be obtained in alco-
hol with stannous chloride or ammonium sulfide or in aqueous alcohol
with sodium sulfide or sodium hydrosulfite. Because of the large heat
effect, the rate must be controlled so that the reaction will not get out
of hand.

When the reducing agent is iron and water, it is necessary for iron
chloride to be present. The mixture must be heated for some time.
The iron chloride usually is obtained by adding a small amount of hy-
drochloric acid, about 5% of theoretical. The reaction is accelerated
by the presence of ammonium chloride.

When the reducing agent is tin and hydrochloric acid, control is ac-
complished by adding the acid in portions to the reaction mixture, as
in the usual reductions with tin and hydrochloric acid (Experiment
33–1). However, accumulation of acid, which happens when the tem-
perature is too low, must be avoided because the reaction is liable to
get out of control, and also because of side reactions. Thus the initial
temperature must be such that the first portion of acid reacts almost
completely before more is added, usually not below 50° to 70°. Of
course, control can be accomplished by adding either tin or the nitro
compound to the other two, but side reactions are most extensive when
the acid concentration is high.

When sodium hydrosulfite is the reducing agent, it is added in por-
tions if the resulting system is homogeneous, as in the reduction of o-
nitrophenol (Experiment 33–2).

Direct hydrogenation takes place only in the presence of a catalyst.
Catalysts that permit the reduction to proceed at ordinary temperature
and pressure, such as platinum, palladium, and active forms of nickel,
are easily poisoned by small amounts of impurities, especially sulfur
compounds. Less active catalysts, for example metallic iron, are not

so easily poisoned, but higher temperatures and pressures are necessary. Agitation must be violent since one reactant is a gas and the catalyst is a solid.

33.15 Completeness of Reaction. If the nitro compound is insoluble in water, completion of reaction with an acidic reducing agent is indicated by the complete solution of the compound in water. Dilution may be necessary, in case the salt of the amine is not very soluble. If alcohol or some other organic solvent has been added to increase the solubility of the nitro compound, a test for completion often can be made by adding a few drops of the mixture to dilute aqueous acid, provided the amount of solvent is not too great. A cloudiness indicates that the reaction is not complete. Naturally, these tests are not valid if the nitro compound is soluble in water.

33.16 Side Reactions. The principal side reactions are: (1) formation of products of a reduction state intermediate between the nitro and amino states, (2) formation of aminophenols, (3) replacement of hydrogen by halogen, (4) replacement of halogen by hydrogen or other groups, and (5) formation of sulfamic acids.

The formation of secondary-reduction products, such as azoxybenzene, azobenzene, or hydrazobenzene, is prevalent in the reduction with metals under alkaline conditions. However, ammonium sulfide, sodium sulfide, and sodium hydrosulfite usually give the desired product.

The formation of aminophenols takes place in the reduction with a metal and acid and becomes more important as the concentration of the acid is increased since the reaction is acid-catalyzed. This takes place through a molecular rearrangement of the intermediate phenylhydroxylamine.

$$C_6H_5NO_2 + 4[H] \rightarrow C_6H_5NHOH + H_2O$$

$$C_6H_5NHOH + H_3O^+ \rightarrow p\text{-}HOC_6H_4NH_3^+ + H_2O$$
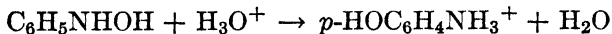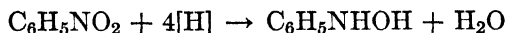
This type of reaction is possible whenever the *para* position is open. In order to keep the acid concentration low it is desirable that each portion of acid react before more is added. Thus, when the rate is low at room temperature, heating is desirable, or, if the system is heterogeneous, agitation must be carried out continuously.

Sometimes chlorine enters the ring when hydrochloric acid is present. Reduction of *o*-nitrotoluene with tin and hydrochloric acid gives a mixture of the desired amine and 2-amino-5-chlorotoluene. This type of side reaction often occurs with tin, stannous chloride, and zinc. Zinc is the worst offender. The product is usually dark colored also. If possible, some other acid, as for example sulfuric or acetic acid, should be used in place of hydrochloric acid.

Halogen atoms *ortho* to nitro groups may be replaced by hydrogen or rarely by other radicals. Stannous chloride and *o*-bromonitrobenzene give aniline, as well as *o*-bromoaniline. This type of reaction is liable to occur with tin, stannous chloride, and zinc; less likely with iron. Halogen atoms in general may be replaced by reduction with hydrogen and a palladium catalyst. Ammonium and sodium sulfides yield sulfur-containing amines with a nitro compound having a halogen or nitro group in the *ortho* position.

A side reaction that accompanies reduction with sodium hydrosulfite is the formation of a sulfamic acid, probably by a reaction of the intermediate hydroxylamine with sodium bisulfite:

$$C_6H_5NH{-}OH + HO{-}SO{-}ONa \rightarrow C_6H_5NH{-}SO_2{-}ONa + H_2O$$
<div align="center">sodium phenylsulfamate</div>
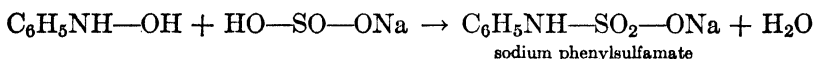
Many sulfamic acids and their salts are soluble in water, and thus material is lost unless the sulfamic acid is hydrolyzed by heating with water. In order to minimize this side reaction the reduction should be carried out as rapidly as possible, as in Experiment 33–2, The Preparation of *o*-Aminophenol.

33.17 Comparison and Recovery. Direct hydrogenation offers the least complication in recovery. For purification, often removal of the catalyst by filtration suffices, before distilling off any solvent.

When ammonium sulfide is the reducing agent, recovery of the amine is comparatively simple, for the excess of reactant can be decomposed merely by heating, thus leaving behind water, the amine, and sulfur, the last of which results from the decomposition of the polysulfide. The sulfur is finely divided, but usually it changes to a more compact form on heating.

Volatile amines often are separated from reaction mixtures by steam distillation. This procedure is indicated when solvent extraction is impractical, as for example in mixtures containing insoluble solids, such as iron oxide and tin hydroxides, which are present respectively after reduction with iron and tin (or stannous chloride). It is necessary to add an amount of strong base which is an excess over any acid added during the reduction operation. If the amount of strong base is insufficient to neutralize the acid, the unneutralized acid will be distributed between the weak bases present, which are the desired amine and the metallic oxide. This hinders the recovery of the amine. Actually an excess of base usually is added, for it is desirable to decrease the amount of solid by dissolving the tin hydroxides.

Solvent extraction of an amine from a reaction mixture is possible only if the mixture is neutral or basic and is not practical if insoluble

compounds are present. However, oftentimes troublesome emulsions are encountered. The solvent should be low boiling, for example ethyl ether. Extraction is more convenient than steam distillation and is feasible when the reducing agent is metallic zinc or sodium hydrosulfite.

Sometimes solvent extraction of the aqueous portion of the distillate in steam distillation is desirable, as in Experiment 33–1, The Preparation of Aniline. In case alcohol or some other water-soluble solvent had been added for the purpose of increasing the solubility of the original nitro compound, it should be removed by distillation or evaporation from the acidic reaction mixture before the base is added.

Crystallization of a solid amine or of an amine salt often is possible if the other reaction products can be kept in solution, as for example when the reducing agent is metallic zinc or tin, stannous chloride or sodium hydrosulfite. In Experiment 33–2, o-aminophenol crystallizes from an aqueous solution containing sodium bisulfite. Sulfates of amines usually are not soluble in water; hydrochlorides, though much more soluble, often separate well when an excess of hydrochloric acid is added.

Oxidation of amines takes place slowly on exposure to air, producing a dark color. This takes place most readily with the most reactive amines, less readily with less reactive amines, for example nitranilines, and least readily with the salts of the amines. Thus the reaction with a given amine is accelerated under basic and retarded under acidic conditions. Darkening involves some loss which however is not great since the oxidation products usually are intensely colored. Distillation of volatile amines is the best method of purification, because the colored compounds have much higher molecular weights. Darkening is especially troublesome in Experiment 33–2, the Preparation of o-Aminophenol.

Experiment 33–1   Preparation of Aniline

In a 1-liter round-bottomed flask provided with an air condenser (Note 1) place 0.20 mole of nitrobenzene (*Caution:* Notes 2 and 3) and 0.4 g. at. wt. of mossy tin. Measure sufficient technical concentrated hydrochloric acid (Note 4) to furnish about 25% excess over the amount required theoretically. Add 10 ml. Agitate carefully, so as not to break the flask, and *essentially continuously*. The mixture should become warm at once. If it does not, apply heat. Add the rest of the acid, at first in 10-ml. portions and later in larger portions. Agitate *essentially continuously* throughout the addition of the acid. Be sure that most of each portion of acid has reacted before adding the next

(Note 5).   Moderate cooling may be advisable if the liquid boils. Finally heat on a steam bath, shaking frequently, until the nitrobenzene has reacted completely (Notes 6 and 7).   More acid may be added, in case the amount seems to be insufficient.   After reduction is complete, let the mixture cool.   A double salt of anilium chloride and stannic chloride, $C_6H_5NH_3Cl \cdot SnCl_4$, may crystallize.

Assemble an apparatus for steam distillation, so that the 1-liter flask can be attached to it (refer to Chapter 10).   Dissolve in 200 ml. of water an amount of sodium hydroxide that is a good excess, 20% or more, over the amount of hydrochloric acid added.   Add this, cold, with thorough agitation, to the reaction mixture, also cold, cooling moderately if the liquid boils.   Steam distil.   At first a two-phase distillate is obtained; later a single-phase distillate.   Collect enough of this, *ca.* 200 ml., to be sure that practically all aniline has distilled (Note 8).   Add solid sodium chloride to the distillate in amount sufficient to produce a half-saturated solution (Note 9).

Extract three times with ethyl ether, using a total of 200 to 400 ml. (refer to Chapter 6).   Dry the ether with a suitable drying agent (refer to Tables 12–2 and 12–3).   Strip off the ether, using a flask of proper capacity to hold adequately the expected amount of product (refer to Subsection 9.15), heating by means of a water bath at a relatively low temperature, *ca.* 50° until most of the ether has been removed (*Caution:* See Experiment 22–1, Notes 1 and 4).   Finally, above 100°, use a shorter condenser.   Collect the desired product in a 5° range near the boiling point of aniline, taking cuts if much material distils ahead of this, and refractionating in systematic fashion.   Calculate the percentage yield (Note 10).

Notes

1. Refer to Subsection 7.21 in regard to air condensers.
2. Both nitrobenzene and aniline are poisons; avoid breathing the vapor and spilling the liquids on the skin.
3. This procedure serves to prepare other amino compounds that can be steam-distilled, for example the toluidines.
4. Technical hydrochloric acid may be 20° Be. or 22° Be., 32% or 35% acid, respectively.   The acid need not be pure.
5. See discussion on the effect of a higher concentration of acid.
6. No drops of nitrobenzene should be visible, and a clear solution should result when a few drops of the liquid are added to about 5 ml. of distilled water.
7. If there is any doubt about this, the mixture can be steam-distilled at this point. If any nitrobenzene is present, the distillation is continued until the distillate is clear.
8. Aniline is slightly soluble in water.
9. Refer to Subsection 6.12, Salting Out.
10. The correct boiling point is 184.5°.   The yield is 90%

Questions

1. How much of the tin is in the stannous form after all the metallic tin has dissolved and reduction has been completed?

2. Why not keep the reaction mixture cold while adding the hydrochloric acid?

3. What side reaction may become important if the concentration of the acid is high?

4. What precipitate is formed when the sodium hydroxide is added to the reaction mixture?

5. Why should the amount of base added be sufficient to neutralize all the original acid?

6. Why is an excess of base desirable?

7. Why is an inorganic salt added to the distillate?

8. Why not extract the alkaline reaction mixture with ether?

9. Does the mixture of steam and aniline vapor come over above or below the boiling point of water?

10. What determines the ratio of the weight of water to aniline at the beginning of the steam distillation?

11. What other reagent could be used for the reduction of nitrobenzene?

12. What is the main impurity in the final product?

13. How can it be removed?

Experiment 33–2 · Preparation of o-Aminophenol (Notes 1 and 2)

In a 500-ml. conical flask place 0.10 mole of o-nitrophenol, 50 ml. of water, and 0.12 mole of sodium hydroxide. Heat until the solids have dissolved (about 60°). Weigh out three portions of sodium hydrosulfite (Note 3), of which two are each one-half the theoretical amount and the third corresponds to a 20% excess, based on 100% purity. Have ready also a warm solution (*ca.* 50°) of 0.08 mole of sodium hydroxide in 25 ml. of water. To the red solution at about 60° add one half the theoretical amount of sodium hydrosulfite gradually over a period of about 0.5 to 1 minute, cooling the solution moderately in case the contents begin to boil (Notes 4 and 5). Agitate continuously to promote rapid solution of the solid. Add the second portion of sodium hydroxide solution (Note 6) and then sodium hydrosulfite, as before, until the theoretical amount has been added. Then with the slurry of liquid and solid at 60° to 70°, add 25 ml. of alcohol, washing down any material near the top of the flask (Note 7). Any decided yellow color and any reddish particles of o-nitrophenol should disappear, thus indicating the completion of the reduction. If any remains, add more hydrosulfite in small portions until there is no more reaction. The reduction should be carried out in 3 to 5 minutes. The final reaction mixture should be only slightly colored; otherwise, the yield is low.

At once add about 175 ml. of alcohol (Note 8) to the still warm liquid (50° to 60°), cool quickly to about 20°, and agitate for 2 or 3 minutes to aid crystallization of salts still in solution (Note 9). Filter through a *clean* Buechner funnel, avoiding needless suction of air through the filter cake (Note 10). Discard this after washing with 50 to 100 ml. of warm alcohol, in 2 or 3 portions (refer to 5.42).

Add 100 ml. of water to the combined filtrates, and distil (Note 11), so as to remove alcohol and leave only water. The final volume should not be less than 150 ml. (Note 12). Add a pinch of sodium hydrosulfite during the distillation if the liquid darkens. If cloudy, filter hot into a beaker; if clear transfer to the beaker, and cool rapidly in an ice pack. Stir until cooled to about 4°, collect on a small clean Buechner or Hirsch funnel, and wash well with a small amount (5 ml.) of water. Dry quickly and *completely* by pressing between absorbent paper or onto porous tile of excellent absorbing properties, removing the solid to another dry surface after one has become wet (Note 2). Obtain a second less pure crop from the filtrate, as before, after evaporating (in a flask) to about 50 ml. After each crop is thoroughly dry, take the melting point, and calculate the percentage yield (Note 13).

Notes

1. The preparation of *o*-aminophenol by the usual methods of reduction is not satisfactory. In order to obtain satisfactory results with sodium hydrosulfite it is essential that the reduction be carried out rapidly, in 5 minutes or less, and that exposure to air be a minimum. To facilitate operations have all materials and apparatus ready before starting. The experiment should be completed in 1 to 1.5 hour.

2. Dry solid *o*-aminophenol is relatively stable toward oxygen. However, in aqueous solution it is oxidized to colored products by air. Oxidation is especially rapid under alkaline conditions. The moist solid turns dark on exposure to air.

3. Sodium hydrosulfite (sodium dithionite, $Na_2S_2O_4$) deteriorates on standing, owing to oxidation by the air. The technical product, usually 94% pure, is satisfactory. The 20% excess usually is sufficient.

4. *o*-Nitrophenol is volatile with steam.

5. If the temperature of the reaction mixture does not increase markedly, the hydrosulfite is unsatisfactory.

6. The solution should not become alkaline (Note 2). Only one-half the base is added at the start because of this fact and also because the sodium salt of *o*-nitrophenol separates. If more than 0.2 mole of sodium hydroxide is taken altogether, a second liquid phase may form when the alcohol is added later.

7. The last portion of the nitrophenol reacts much more rapidly after the addition of the alcohol, because of the better solvent action of the alcohol. If more than 25 ml. of alcohol is added, some sodium hydrosulfite may be thrown out of solution along with the sulfite.

8. If preferred, methanol may replace ethanol.

9. Solubilities of *o*-aminophenol, grams per 100 g. of solvent, are: in water, 1.7 at 0°, 3.0 at 80°, and 7.1 at 100°; in ethyl alcohol, 4.3 at 0°. The addition of alcohol decreases the solubility of inorganic salts and increases the solubility of *o*-aminophenol.

10. Contact with the air (see Note 2) is minimized by using a funnel just large enough to hold the solid, by regulating the suction carefully, and by frequent pressing of the filter cake.

11. Distillation is preferred to evaporation, in order to prevent access of air.

12. As the alcohol is driven out of the solution, the solubility of *o*-aminophenol decreases, and that of the sodium salt present increases (Question 8).

13. The melting point of carefully purified *o*-aminophenol is 177° (cor.) when introduced into the hot bath. It decomposes below this temperature. Usual figures range between 170° and 174°. Yield, 55%.

Questions

1. What is the reaction between oxygen and sodium hydrosulfite in aqueous solution?

2. What are the inorganic salts that separate when alcohol is added?

3. What other reducing agents are employed for reducing organic nitro compounds?

4. Why does *o*-nitrophenol separate as the reaction proceeds?

5. Why does *o*-nitrophenol distil with steam, whereas *p*-nitrophenol does not?

6. What is the function of the sodium hydroxide?

7. Why does the addition of a small amount of alcohol aid the reaction?

8. Calculate the amount of boiling water necessary to dissolve 0.1 mole of *o*-aminophenol.

9. What is a possible oxidation product of *o*-aminophenol?

10. Is *o*-aminophenol more easily oxidized than aniline? than phenol?

11. What are the main impurities in the final product?

Experiment 33–3   Properties of Aromatic Amines

A   SOLUBILITY.   Test the solubility in water of aniline (or a toluidine) and of sulfanilic acid by shaking about 1 g. of the amine with 5 ml. of water. Add to the resulting mixture from a dropper 1 to 2 ml. of 6 *N* hydrochloric acid. To acidified contents add 3 to 5 ml. of 6 *N* sodium hydroxide.

B   ACETYLATION.   To 0.1 g. (2 or 3 drops) of aniline, or of some other aromatic amine, add 4 to 5 drops of good acetic anhydride (Note 1), and heat to *ca.* 100° for a few minutes. Add 2 or 3 ml. of water to remove the acetic acid, stir well, remove the water with a dropper, and repeat. A solid should remain. Crystallize this from hot water (Note 2). Determine the melting point.

Repeat with an unknown amine, which may be obtained from the instructor.

C HINSBERG TEST. Shake 2 to 3 drops of aniline, N-methylaniline, and N, N-dimethylaniline separately with 6 to 9 drops of benzenesulfonyl chloride, 4 to 5 ml. of water, and 2 ml. of 3 N sodium hydroxide, until the benzenesulfonyl chloride has reacted. Add hydrochloric acid in excess. Note the difference in behavior.

D BROMINATION. Obtain a clear aqueous solution of aniline by shaking about 0.5 ml. with 10 ml. of water and filtering through filter paper previously wet with water. Add bromine *water* to the filtrate until there is an excess and then a few crystals of sodium bisulfite to remove excess bromine.

E OXIDATION. Separately test the effect of chromic acid mixture (refer to 25.14) and of aqueous permanganate on aniline (use 1 or 2 drops) and on *o*-aminophenol. Test the effect of silver nitrate and of ammoniacal silver nitrate (Note 3) on these two amines.

Notes

1. This deteriorates rapidly when exposed to moisture in the air.
2. The hydrolysis of acetanilide by hot water although slow becomes fairly rapid in strong acid.
3. The ammoniacal silver solution should not be kept. (See Experiment 25–5, Note 3.)

Questions

1. Explain the solubility behavior of amino compounds in A.
2. Why is it desirable to remove acetic acid before crystallizing in B?
3. Do you think the product you obtained in B is pure?
4. Why is a test like this of value?
5. Compare the behavior of the three amines in the Hinsberg test. How do you account for the differences?
6. What other aromatic compound have you brominated?
7. Did it brominate as easily as aniline? Explain.
8. How do benzene and aniline compare in ease of oxidation?
9. Write equations for the reactions in B, C and D.
10. What is an approximate value of ΔH for the rearrangement of phenylhydroxylamine to *p*-aminophenol?
11. According to the data of Table 1–4, can ferrous ion reduce nitrobenzene in 1 N hydrochloric acid? in 0.001 N hydrochloric acid? Refer also to 38.11.

Chapter 34

AROMATIC DIAZONIUM COMPOUNDS

The diazonium compounds are very important in the aromatic series because they undergo a large variety of replacement reactions and also couple with a large number of amines and phenols to produce azo dyes.

SECTION 34.1 PREPARATION OF DIAZONIUM COMPOUNDS

Diazonium salts may be prepared by the action of (a) an acid on an aqueous solution of sodium nitrite and an amine salt, (b) nitrous anhydride on an amine salt, (c) butyl (or amyl) nitrite on an alcoholic solution of an amine salt in the presence of a trace of strong acid, or on an acetic acid solution of the amine, (d) nitrosyl sulfuric acid on an amine (or amine sulfate):

(a) $$C_6H_5NH_2 + HCl \rightarrow C_6H_5NH_3Cl$$

$$NaNO_2 + HCl \rightarrow HNO_2 + NaCl$$

$$C_6H_5NH_3Cl + HNO_2 \rightarrow C_6H_5N_2Cl + 2H_2O$$

$$\overline{C_6H_5NH_2 + NaNO_2 + 2HCl \rightarrow C_6H_5N_2Cl + NaCl + 2H_2O}$$

(b) $$2C_6H_5NH_3Cl + N_2O_3 \rightarrow 2C_6H_5N_2Cl + 3H_2O$$

(c) $$C_6H_5NH_3Cl + C_4H_9ONO \rightarrow C_6H_5N_2Cl + C_4H_9OH + H_2O$$

(d) $$2H_2SO_4 + NaNO_2 \rightarrow ONOSO_3H + H_2O + NaHSO_4$$

$$C_6H_5N{=}NC_6H_4NH_2 + ONOSO_3H \rightarrow$$

$$C_6H_5N{=}NC_6H_4N_2SO_4H + H_2O$$
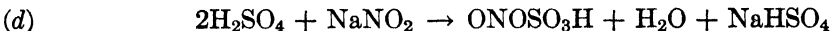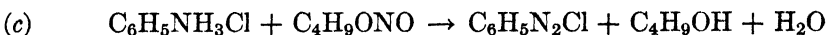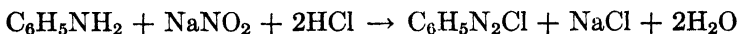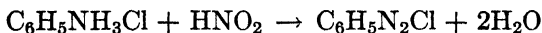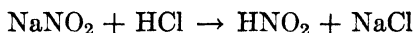
Method a is used with amines which diazotize easily and when isolation of the diazonium salt is not necessary. This is the usual method, for generally the subsequent reaction of the diazonium salt is carried out in aqueous solution. Methods b and c are useful mainly in the preparation of dry diazonium salts or when it is desirable to carry out the reaction in the absence of water. Method d is useful when the amine cannot be diazotized by the other methods.

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34.11 Thermochemistry. The nature of the heat effect in the formation of benzenediazonium chloride from aniline hydrochloride, sodium nitrite, and hydrochloric acid cannot be calculated by means of bond energies, for the values of all the types of bonds involved are not known. Actual measurement of the heat effect in individual reactions shows that ΔH for the over-all reaction is about -25 kcal. The reaction therefore is decidedly exothermic. Since nitrous acid is unstable at room temperature, the necessity of having efficient cooling is at once evident.

34.12 Effect of Substituents on the Rate. The diazotization of aniline in aqueous solution is very fast, even at $0°$. When sodium nitrite is added to a large excess of an aniline salt in cold aqueous acid, the reaction is so rapid that the nitrous acid has reacted by the time a sample can be removed and tested for unreacted nitrous acid. The reaction actually is between nitrous acid and the positive ion of the amine salt. The influence of a substituent operates through its effect on the basicity of the amino group. Thus in dilute acid solution a negative substituent decreases the rate of diazotization, although the rate of diazotization of the amine salt is actually increased by a negative substituent. The rates are in the orders: $NO_2 < SO_3H < COOH < Cl$ and $o\text{-} < p\text{-} < m\text{-}$. Alkyl and alkoxy groups have little or no effect. 2,4,6-Trinitroaniline is such a weak base that it cannot be diazotized in aqueous solution, even when the acid concentration is high. Hydrolysis of the salt of the amine, which becomes more important with the weaker bases, is the factor mainly responsible for difficulty of diazotization in aqueous solution. (method a). Hydrolysis is largely eliminated in the other methods, since then the water concentration can be kept low.

34.13 Diazotization in Aqueous Solution. In method a the effect on the rate by the different acids is in the order:

$$HBr > HCl > HNO_3, \ H_2SO_4 \quad \text{and} \quad 1,5\text{-}C_{10}H_6(SO_3H)_2$$

In general, in acid solution the rate increases as the acid concentration rises. At $10°$ the rate is three to four times greater than at $0°$. However, the temperature cannot be raised very much above room temperature because nitrous acid decomposes even at $0°$. Unless the amine diazotizes with difficulty the temperature usually is near $0°$. A disadvantage of aqueous sulfuric acid is the fact that it may form an insoluble salt with the amine. An advantage in the use of a somewhat soluble salt is the ability to follow the course of the reaction visibly, provided, of course, that the diazonium salt is soluble, as usually is the case.

In method a a minimum of 2.5 moles of acid usually is taken per mole of base. The excess 0.5 mole is necessary to prevent hydrolysis and to diminish the side reaction of coupling. In case the amine is not easily diazotized, as for example p-nitraniline, the naphthylamines, and the benzidine bases, a larger excess of acid is necessary, as in Experiment 34–3, and usually a higher temperature, 10° to 20°, is desirable; otherwise, the coupling reaction may become extensive. Since the concentration of acid is important the solution should not be too dilute.

There are two modifications: the **direct method,** in which a solution of sodium or potassium nitrite is added to the acid solution or suspension of the amine salt, and the **invert method,** in which a neutral or alkaline solution containing dissolved sodium nitrite and the amino compound is added to the acid, or the acid is added all at once to this solution. In order to employ the invert method the amino compound must possess some other functional group, as for example the sulfonic acid or carboxyl group, which can form salts with bases.

To minimize side reactions the diazotization is carried out as rapidly as consistent with control of temperature by adding the nitrite rapidly in the direct method or the acid rapidly in the invert method. Temperature control is easiest by internal cooling, that is, by adding ice directly to the reaction mixture. However, this has the disadvantage of dilution, which decreases the acid concentration, thus increasing the hydrolysis of the amine salt. A decrease in the rate of diazotization and an increase in the rate of coupling may result (see Section 34.3). Sodium and potassium nitrites seldom are 100% pure, since they may contain as much as 15% water. Technical nitrite may contain 1 to 3% nitrate.

Often the salt of the amine is insoluble or only sparingly soluble in water. It is important that it be in the form of a fine loose crystal meal. This can be obtained by rapidly cooling, while agitating, a hot saturated or nearly saturated aqueous solution of the salt. In this form the salt dissolves readily as the nitrite is added. If the individual crystals are large or if the fine precipitate has clumped together, diazotization is liable to be slow even when an excess of nitrous acid is present. This is undesirable because nitrous acid sometimes causes decomposition of the diazonium salt. When dissolving the amine salt, usually more than one equivalent of acid must be added to the amine to overcome hydrolysis, which is greater, the weaker the basic strength of the amine. However, the excess should be kept to a minimum because the solubility of the salt drops rapidly with excess acid. Any additional excess acid needed should be added after the amine has been dissolved.

34.14   Diazotization with Nitrous Anhydride or with Alkyl Nitrites.   In methods *b* and *c*, the salt of the amine is suspended or dissolved in alcohol, then nitrous anhydride or an alkyl nitrite is added, and the diazonium salt is precipitated by the addition of ether.   Some danger attends this procedure because many solid diazonium salts, especially hydrohalides, decompose explosively when dry.   However, a large number of salts with sulfuric or a naphthalene sulfonic acid are quite stable.

34.15   Diazotization with Nitrosylsulfuric Acid.   In method *d* the amine is dissolved in sulfuric, glacial acetic, or phosphoric acid. To this is added nitrosylsulfuric acid, obtained by adding sodium nitrite to sulfuric acid.   The advantages of this method are: (1) Salt formation, even of very weak bases, is more complete, since no water is present; (2) the reaction can be accelerated by temperature increase since nitrosylsulfuric acid is stable, even at 80°.   It is possible by this procedure to diazotize amines that are very resistant to the other methods, as for example 2,4,6-trinitroaniline and *p*-aminoazobenzene (Experiment 34–5).   Also, some diamines can be converted to tetrazo compounds.

34.16   Completion of Reaction.   Starch–iodide paper is used to detect excess of nitrous acid, which causes an immediate color.   This test must not be confused with the color that develops slowly when the paper is acidified.   In method *a* the test need not be made until about 90% of the nitrite has been added.   When the rate is low, as near the end of the reaction when the concentration of the amine salt is low, the final test must not be made too soon after the addition of nitrite. In method *d* naturally the test portion must be well diluted before contact is made with the starch–iodide paper.   Sometimes in method *d* merely dilution with water is sufficient, since the unchanged amine may give a precipitate of free amine or of amine sulfate.

An excess of nitrite should be avoided, especially in those cases where it reacts with substances added later, as for example potassium iodide, cuprous chloride, phenol, and dimethylaniline.   The diazonium compounds themselves often decompose more rapidly in aqueous solution when nitrous acid is present.   Excess nitrous acid can be removed by adding urea or sulfamic acid.   However the reaction is slow, especially when the acid concentration is low.

Starch–iodide paper is made by dipping filter paper in starch paste containing potassium iodide and drying the paper.   Instead one may use starch paper, made similarly from starch paste, and just before use dip it in a dilute (about 1%) solution of potassium iodide.   This

probably is more reliable, since sometimes starch–iodide paper deteriorates.

34.17 Side Reactions. One of the principal side reactions is that of coupling of the diazonium compound with unreacted amine, to produce a diazoamino or a highly colored aminoazo compound (see Section 34.3). The former usually precipitates out. These reactions become troublesome if the acid concentration is too low, or if the diazotization is carried out too slowly.

Intramolecular coupling may take place when an amino or hydroxyl group is *ortho* to the amino group being diazotized. This results in the formation of a heterocyclic ring. Thus *o*-phenylenediamine is converted to benzotriazole, and *o*-aminophenol to *o*-azophenol oxide (benzoxdiazole):

benzotriazole

benzoxdiazole
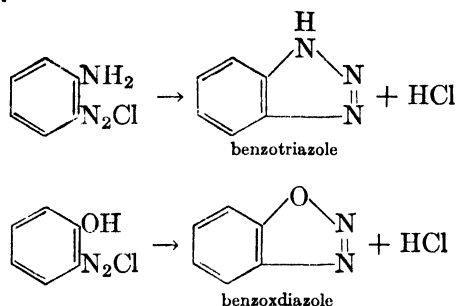
The other principal side reaction is decomposition in aqueous solution to nitrogen and the corresponding phenol. Benzenediazonium chloride is fairly stable at 0° but decomposes rapidly at 60°. The diazonium salts obtained from *o*-toluidine, *m*-toluidine and *m*-phenylenediamine are less stable, whereas those from *p*-toluidine and amines having negative substituents on the benzene ring, such as carboxy, hydroxy, methoxy, halogen, and nitro groups, are more stable in aqueous solution. Some even resist water at 100°.

Another side reaction is replacement of the diazonium group by halogen, from a reaction with a hydrogen halide. Hydriodic acid reacts rapidly, but hydrobromic and hydrochloric acids usually only slowly, even when heated. To avoid this complication the diazotization often is carried out in a sulfuric acid solution.

Certain groups, for example alkoxy, nitro, chloro, and the sulfonic group, when in the *ortho* position to the amino group sometimes are eliminated during diazotization. The products are diazo oxides and are the ones that would be formed if the eliminated groups were replaced by the hydroxyl group.

34.18   Stabilization of Diazonium Salts.   Generally, insoluble salts are precipitated when a naphthalene sulfonic acid or a soluble salt of a naphthalene sulfonic acid is added to the solution of the diazotized amine.   Many such salts are stable and can be kept for long periods of time, even if dry.   The stability is greater if excess acid is present. Insoluble diazonium fluoborates are precipitated when an aqueous solution of fluoboric acid or its sodium salt is added to the aqueous diazonium solution.   Many fluoborates are stable dry.

SECTION 34.2   REPLACEMENT REACTIONS

The most important replacement reactions are replacement by (a) hydrogen, (b) alkoxy, (c) hydroxy, (d) halogen, (e) cyano.

(a) $C_2H_5OH + C_6H_5N_2Cl \rightarrow C_6H_6 + N_2 + CH_3CHO + HCl$

$Na_2SnO_2 + NaOH + C_6H_5N_2Cl \rightarrow$

$$C_6H_6 + N_2 + Na_2SnO_3 + NaCl$$

(b) $CH_3OH + C_6H_5N_2Cl \rightarrow C_6H_5OCH_3 + N_2 + HCl$

(c) $HOH + C_6H_5N_2Cl \rightarrow C_6H_5OH + N_2 + HCl$

(d) $HI + C_6H_5N_2Cl \rightarrow C_6H_5I + N_2 + HCl$

$CuCl + C_6H_5N_2Cl \rightarrow C_6H_5Cl + N_2 + CuCl$

$CuBr + C_6H_5N_2Br \rightarrow C_6H_5Br + N_2 + CuBr$

$NaBF_4 + C_6H_5N_2Cl \rightarrow C_6H_5N_2BF_4 + NaCl$

$C_6H_5N_2BF_4 \rightarrow C_6H_5F + N_2 + BF_3$

(e) $CuCN + C_6H_5N_2Cl \rightarrow C_6H_5CN + N_2 + CuCl$
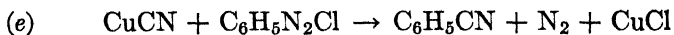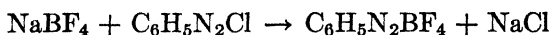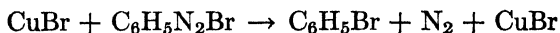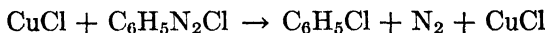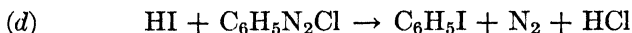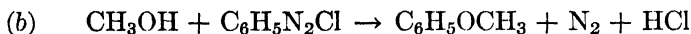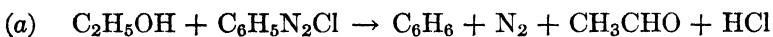
34.21   Replacement by Hydrogen and by Alkoxy Radicals.   The diazonium group may be replaced by hydrogen by the use of certain reducing agents, as for example an alcohol, sodium stannite, or hypophosphorous acid.   If an easily reducible group such as a nitro group is attached to the benzene ring, it may suffer reduction also.   Alcohol has the advantage that ordinarily it does not reduce a nitro group.

When the diazonium salt is heated with alcohol, the diazo group is replaced by alkoxyl.   Some hydrocarbon is also formed at the same time.   The reaction is influenced by the nature of the diazonium compound, the alcohol, and the pressure and temperature.   Negative groups like halogen, nitro, and carboxyl favor replacement by hydrogen, especially when in the *ortho* position.   The higher alcohols aid hydrocarbon

formation. The yield of ether from benzenediazonium sulfate for dif-
ferent alcohols is: methyl 70%; ethyl 60%; propyl 50%; active amyl
30%. Yields of hydrocarbon may be increased by the addition of
sodium alkoxide, alkali, or zinc dust. High pressures and temperature
aid ether formation. Hydrocarbon formation is favored by using dia-
zonium salts stabilized by naphthalene sulfonic acid. In fact, this is
an elegant method for replacing the diazonium group by hydrogen.

34.22 Replacement by the Hydroxyl Group. The rate of reac-
tion of diazonium salts to form phenols by the action of water is increased
by heating, as in the preparation of phenol (Experiment 35–2). The
influence of substituents has already been mentioned under side reac-
tions. The more stable salts may be hydrolyzed by heating with 80%
sulfuric acid or with an aqueous solution of sulfuric acid and sodium
bisulfate at temperatures of 150° to 170°. Often the reaction can be
carried out at temperatures below 100° by the addition of copper sulfate.
A side reaction is the coupling of the diazonium salt with the phenol,
which is especially important in the case of the stable diazonium salts.
This can be minimized by dilution, or by removal of the phenol as
formed, either by steam distillation, or by extraction with a suitable
solvent.

34.23 Replacement by Halogen Atoms. When hydriodic acid or
an alkali iodide is added to a solution of benzenediazonium chloride,
iodobenzene is formed in good yield. Bromo- and chlorobenzene are
formed only in small amount by analogous treatment, even when
heated. In general diazonium iodides decompose similarly, but bro-
mides and chlorides do not. However, yields usually are satisfactory
in the presence of certain catalysts, for example the corresponding
cuprous halide (Sandmeyer reaction) or copper powder (Gattermann
reaction). These are added to the diazonium bromide or chloride solu-
tion. The cuprous halide should be freshly prepared and then dissolved
either in hydrobromic or hydrochloric acid to form the respective halo-
cuprous acid, $HCuBr_2$ or $HCuCl_2$. When this is added to the solution
of the diazonium salt, an addition compound usually separates. This
decomposes when heated to yield the desired product. Chlorotoluene
and bromotoluene are prepared this way (Experiment 34–1). Replace-
ment by fluorine is best accomplished by heating the dry diazonium
fluoborate (Experiment 34–1).

34.24 Replacement by the Cyano Group. This takes place when
the solution of the diazotized amine is added to a solution of sodium
(or potassium) cyanide, followed by the addition of copper powder in
the cold (Gattermann reaction), or when it is heated with sodium (or
potassium) nickelous or cuprous cyanide. The latter is prepared in

aqueous solution by the reaction of cupric sulfate with the alkali cyanide. Cyanogen is evolved. Nickelous cyanide is preferable to cuprous since sometimes yields are better and no cyanogen is evolved during its preparation.

SECTION 34.3 COUPLING REACTIONS

Diazotized aniline couples fairly rapidly at room temperature with phenols and with aromatic amines in weakly acidic, neutral, or basic solutions. The reactive substance is believed to be the diazonium ion. Negative substituents on the benzene ring of the diazonium ion enhance the ability to couple in acid solution. On the other hand, they increase the tendency for the normal diazotate to pass over into the unreactive isodiazotate in basic solution. In general, the solution should not be strongly basic during coupling.

34.31 Phenols. The coupling of diazotized amines with phenols takes place directly on the ring, producing hydroxyazo compounds. Phenol and diazotized aniline yield p-hydroxyazobenzene.

$$C_6H_5N_2Cl + HC_6H_4OH \rightarrow C_6H_5N\!\!=\!\!NC_6H_4OH + HCl$$
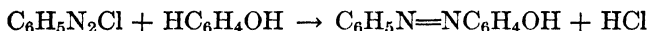
The *para* position is the most reactive, but, if this is occupied, coupling takes place in the *ortho* position. The same relation holds with α-naphthol, but β-naphthol couples only in the adjacent 1-position. Negative substituents in the phenol decrease the ability to couple, whereas alkyl groups increase it. Naphthols couple much more readily than phenol. Coupling takes place especially readily under alkaline conditions. This is in agreement with the observation that phenate ions undergo substitution more readily than the corresponding phenols. Two and sometimes three azo groups can be introduced into phenols, the latter only under strongly alkaline conditions. Phenol ethers also couple but less readily than phenols.

Para red (Experiment 34–3) is prepared by coupling diazotized p-nitraniline with β-naphthol, and Sudan III (Experiment 34–5) by coupling diazotized p-aminoazobenzene with β-naphthol.

. Para red

$$\text{C}_6\text{H}_5\text{N}{=}\text{NC}_6\text{H}_4\text{N}_2\text{SO}_4\text{H} + \underset{\text{HO}}{\text{(naphthol ring)}} \rightarrow$$

$$\text{C}_6\text{H}_5{-}\text{N}{=}\text{N}{-}\text{C}_6\text{H}_4{-}\text{N}{=}\text{N}{-}\underset{\text{HO}}{\text{(naphthol ring)}} + \text{H}_2\text{SO}_4$$

Sudan III
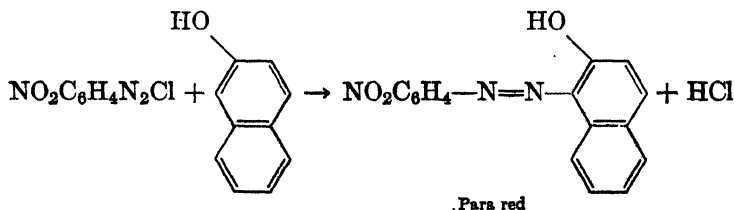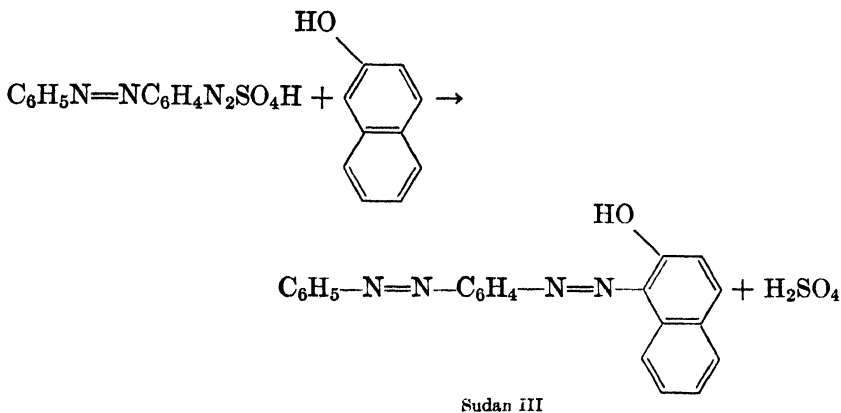
34.32 Amines. Coupling may take place at the amino group or directly on the ring. Benzenediazonium chloride couples with aniline to produce diazoaminobenzene and with *m*-phenylenediamine to produce 2,4-diaminoazobenzene.

$$\text{C}_6\text{H}_5\text{N}_2\text{Cl} + \text{H}_2\text{NC}_6\text{H}_5 \rightarrow \text{C}_6\text{H}_5\text{N}{=}\text{NNHC}_6\text{H}_5 + \text{HCl}$$
diazoaminobenzene

$$\text{C}_6\text{H}_5\text{N}_2\text{Cl} + \text{C}_6\text{H}_4(\text{NH}_2)_2 \rightarrow \text{C}_6\text{H}_5\text{N}{=}\text{NC}_6\text{H}_3(\text{NH}_2)_2 + \text{HCl}$$
2,4-diaminoazobenzene
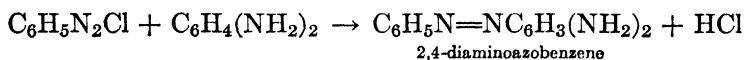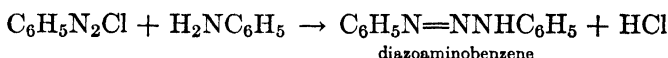
Unless there is a reactive position on the benzene ring, coupling takes place at the amino group. However, many amines couple directly on the ring, owing to the presence of either activating substituents on the ring or two alkyl groups in place of the two hydrogen atoms of the amino group, for example *m*-toluidine, *m*-phenylenediamine, the naphthylamines (*alpha* and *beta*), and dimethylaniline. The positions taken correspond to those taken in the case of the corresponding phenols and naphthols (34.31).

Methyl orange (Experiment 34–2) is obtained by coupling diazotized sulfanilic acid with dimethylaniline. Diazotized sulfanilic acid is prepared by the invert method of diazotizing.

$$1,4\text{-}\overset{+}{\text{H}_3\text{N}}\text{C}_6\text{H}_4\text{SO}_3^- + \text{Na}_2\text{CO}_3 \rightarrow 1,4\text{-H}_2\text{NC}_6\text{H}_4\text{SO}_3\text{Na} + \text{NaHCO}_3$$

$$1,4\text{-H}_2\text{NC}_6\text{H}_4\text{SO}_3\text{Na} + \text{NaNO}_2 + 2\text{HCl} \rightarrow$$
$$1,4\text{-}\overset{+}{\text{N}_2}\text{C}_6\text{H}_4\text{SO}_3^- + 2\text{NaCl} + 2\text{H}_2\text{O}$$

$$(\text{CH}_3)_2\text{NC}_6\text{H}_5 + \overset{+}{\text{N}_2}\text{C}_6\text{H}_4\text{SO}_3^-\text{-}1,4 \rightarrow$$
$$1,4\text{-}(\text{CH}_3)_2\text{N}{-}\text{C}_6\text{H}_4{-}\text{N}{=}\text{N}{-}\text{C}_6\text{H}_4{-}\text{SO}_3\text{H-}1,4$$
methyl orange
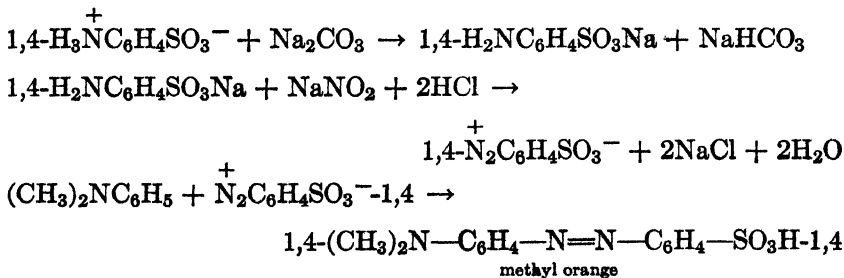
The formation of a diazoamino compound often occurs during diazotization. It can be made the principal reaction if the amounts of nitrite and acid present are one-half the theoretical amount for diazotization. Diazoamino compounds are converted to p-aminoazo compounds (provided, of course, the *para* position is not occupied) when heated under mildly acid conditions such as that obtained by a mixture of the amine and the amine hydrochloride.

Diazoaminobenzene rearranges to p-aminoazobenzene when heated with aniline and aniline hydrochloride.

$$C_6H_5\text{—}N\text{=}N\text{—}NHC_6H_5 \rightarrow C_6H_5\text{—}N\text{=}N\text{—}C_6H_4NH_2$$
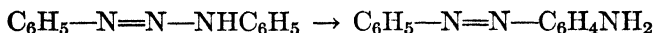
The conditions of the rearrangement must be well controlled in regard to acidity and temperature, for diazoaminobenzene undergoes scission when heated with hydrochloric acid. The initial products are aniline hydrochloride and benzenediazonium chloride. The latter would decompose rapidly, if heated with water alone. The scission probably is one step in the rearrangement. The preparation of p-aminoazobenzene from aniline can be accomplished in one operation without isolating the diazoaminobenzene, as in Experiment 34–4.

Experiment 34–1   General Method of Preparing Aryl Halides by the Sandmeyer Synthesis

p-Chlorotoluene (Note 1)

PREPARATION OF CUPROUS CHLORIDE. To a hot solution of 0.5 mole of copper sulfate and 0.55 or 0.60 mole of sodium chloride in about 0.5 liter of water in a 2-liter flask (Note 2), add with agitation, during a period of a few minutes, a solution of 0.25 mole of sodium bisulfite (or metabisulfite; Note 3) and 0.5 to 0.6 mole of flake caustic soda (Notes 4 and 5) in about 0.2 liter of water. Allow the mixture to cool, decant the liquid, and wash the solid three or four times with water, decanting the solution (Note 6). Dissolve the solid in sufficient commercial 32% hydrochloric acid (sp. gr. 1.16), to furnish about 2 moles of hydrogen chloride. Cool this solution to 0° while the toluidine is being diazotized.

PREPARATION OF TOLUENEDIAZONIUM CHLORIDE. Measure out sufficient concentrated hydrochloric acid to furnish a 25 to 50% excess over the amount required for diazotizing the amine (Note 7). Prepare 0.40 mole of finely divided p-toluidine hydrochloride by: (a) heating 0.40 mole of p-toluidine in a large beaker (0.6 liter or larger) with slightly more than the equivalent amount of concentrated hydrochloric acid

(a part of that measured out), adding somewhat more water and additional small amounts of hydrochloric acid if necessary, until no free toluidine remains and the salt has largely dissolved, hot (Note 8); (b) adding the rest of the acid quickly, while stirring vigorously; (c) cooling rapidly to about 0° by external cooling, and stirring continuously to prevent lumping. Do the heating and dissolving in a reasonably short time, so as to minimize loss due to volatility of the amine.

Add about 150 g. of crushed ice, and then without delay and with stirring add a cold previously prepared solution of 0.42 mole of sodium nitrite in about 100 ml. of water. Add the first three fourths to four fifths during a period of 0.5 to 1 minute and the rest in small portions, until a positive test for excess nitrous acid is obtained with starch–iodide paper. Add ice if necessary, to keep the temperature at 0° to 5°.

DECOMPOSITION, AND RECOVERY OF PRODUCT (Notes 9 and 10). Without needless delay allow the diazonium solution to run into the cold cuprous chloride solution with thorough agitation. An addition compound separates. Keep the mixture at room temperature for 0.5 to 1 hour, mixing occasionally. The mixture may stand overnight, if desired. Attach to an apparatus for steam distillation (refer to Chapter 10). In case the standing time has been about 1 hour or less, heat gradually to 60°; otherwise, the reaction may get out of control. Steam-distil. Separate the p-chlorotoluene, remove any phenolic compound with a suitable reagent (Note 11), and wash with water three or four times. Dry with a suitable drying agent, and distil, collecting over a 3° range (Note 12).

Notes

1. Adapted from *Organic Syntheses*, Collective Volume I, second edition, page 170, John Wiley & Sons, 1944. p-Bromotoluene may be prepared from p-toluidine, hydrobromic acid being used instead of hydrochloric acid, and cuprous bromide instead of cuprous chloride. p-Fluorotoluene and p-iodotoluene are prepared according to Notes 9 and 10, respectively. Isomeric *ortho* compounds may be prepared from o-toluidine, the *meta* from m-toluidine.

2. An open vessel allows easy access of air. When the decomposition of the diazonium compound is carried out in a flask, this must be large because of gas evolution later.

3. Ordinary sodium bisulfite is usually better than 90% pure.

4. Technical flake caustic soda, about 95% sodium hydroxide, is satisfactory. A purer grade is not necessary.

5. Cupric ion is reduced by sulfite ion, according to the equation:

$$2CuSO_4 + NaHSO_3 + 2NaCl + 3NaOH \rightarrow 2CuCl + 2H_2O + 3Na_2SO_4.$$

6. Cuprous chloride is colorless but is rapidly changed by oxygen to the cupric state. The flask should be kept closed by a stopper to prevent needless access of air.

7. Refer to equations; consult instructor if in doubt; be sure of the concentration of acid.

8. Note that at 100° *p*-toluidine is a liquid and the salt is a solid. Avoid needless dilution. Refer to 34.13. In case a higher molecular-weight amine is to be diazotized, solution is more difficult. A larger volume of water will be needed, and then a larger excess of acid (more than 25%) should be added later. In case recovery of the product by steam distillation is not feasible, due to low vapor pressure, try direct separation of the phases.

9. If fluorotoluene is to be prepared, to the diazonium solution add an aqueous solution of sodium fluoroborate (25 to 50% excess), and stir for 10 to 15 minutes to obtain complete precipitation. Collect the solid by suction filtration, and wash well with cold water. Then wash with alcohol, preferably in a beaker (refer to 5.42), so as to remove water completely. Then wash with ether to remove alcohol. Dry *completely*, preferably in a vacuum desiccator.

In a flask attached to a wide exit tube (O.D. not less than 10 mm.) leading into a layer of crushed ice, about 2 inches deep, in a large (2-liter) flask, decompose the solid by heating with a direct flame, starting at one side. Control the rate of decomposition by the degree of heating. *Caution:* Be sure that boron trifluoride does not leak out of the apparatus into the laboratory and that water does not suck back into the hot flask.

Add some ether, separate the phases, remove any phenolic compound by alkaline extraction, wash well, dry with a suitable drying agent, and recover the product by distillation. Yield 60%.

10. In case iodotoluene is to be prepared, to the cold diazonium solution add an aqueous solution containing some excess of potassium iodide. Allow the solution to stand until the vigorous reaction has subsided. The iodotoluene may be recovered by steam distillation, as with chlorotoluene, or by extraction with ether, as with fluorotoluene. In the latter case, however the mixture should be warmed, to be sure that decomposition is complete. Any free iodine can be removed by extraction with an aqueous base.

Since chlorotoluene is liable to be formed to some extent, the diazotization should be done with sulfuric acid, rather than with hydrochloric acid. The molar relationships remain unchanged, but a larger volume of water will be needed, owing to the lower solubility of the amine sulfate.

11. Although aqueous alkali will extract phenolic compounds, usually emulsification is troublesome. Cold 60 to 80% sulfuric acid is recommended on this account. With alkali, addition of ether usually is necessary. If sulfuric acid is used, it should be well removed before distilling.

12. Usual yield is 70%. Boiling points: *o*-bromotoluene 182°; *p*-bromotoluene 184°; *o*-chlorotoluene 159.5°; *p*-chlorotoluene 161.6°; *o*-fluorotoluene 116°; *p*-fluorotoluene 117°; *o*-iodotoluene 206°. Melting point: *p*-iodotoluene 34.5–35.0°.

Questions

1. What is the theoretical molal ratio of hydrochloric acid to toluidine for the diazotization?

2. Why is the molal ratio of hydrochloric acid to *p*-toluidine not the theoretical ratio?

3. What is the advantage in having the toluidine salt in a finely divided state?

4. Write the structure of toluenediazonium chloride.

5. Why must the solution be kept cool during the diazotization?
6. Why should the diazotization not be done slowly?
7. What is the action of nitrous acid on potassium iodide? Write the equation.
8. Explain why the aromatic diazo compounds are important.
9. What is the difference between the Sandmeyer and the Gattermann syntheses?
10. What groups may replace the diazonium group?
11. What product results from the monochlorination of toluene at 25°, in the presence of iron chloride?
12. How else may p-chlorotoluene be obtained reasonably free of the *ortho* isomer?
13. Why is it better, in the preparation of fluorotoluene, to pass the distillate directly into ice water, rather than through a condenser cooled by ice water?
14. What solid compound can be obtained easily from p-chlorotoluene?
15. What is the main impurity or impurities in the crude and final products?
16. What steps have been taken to remove them?

Experiment 34–2   Preparation of Methyl Orange (Note 1)

Prepare a solution of sodium sulfanilate (in a 250- or 400-ml. beaker) from 0.02 mole of sulfanilic acid in *ca.* 100 ml. of water and a slight excess over 0.02 mole of sodium carbonate (Note 2). Add 0.02 mole of sodium nitrite (Note 3). Cool to *ca.* 5° with outside cooling; add ice (25 to 50 g.) so that the temperature of the solution drops below 0°; then add all at once sufficient hydrochloric acid, cooled to 0°, to furnish an excess of *ca.* 0.01 mole, taking into account the equations involved (Note 4) and the amount of sodium carbonate added. Mix well, and allow to stand for *ca.* 10 minutes.

Prepare a solution of 0.02 mole of dimethylaniline in hydrochloric acid (about 1 N; Note 5). Add this cold to the diazotized sulfanilic acid, mix well, and then with stirring slowly neutralize the excess hydrochloric acid, adding ice to keep the mixture cold (Note 6).

In order to facilitate coagulation, warm to 30° or 40°, preferably in a flask so that air does not have ready access, and keep in continual motion, as by a slowly moving stirrer, for 0.5 to 1 hour.

Collect the solid by suction filtration, removing as much water as possible. Let the solid dry completely, and then remove soluble salts by stirring with much water. Apply suction filtration, and continue washing until the filtrate gives a negative test for chloride ion (Note 7). Dry *completely* before weighing. Determine the percentage yield.

Notes

1. Other indicators of the methyl orange type may be prepared by this procedure. Either dimethylaniline may be replaced by some other tertiary amine, for example, diethylaniline, or sulfanilic acid may be replaced by some other sulfonated primary amine.

2. The excess need not exceed 20%. Warming at this point aids solution.

3. Any excess of nitrous acid may be decomposed by adding urea. Nitrous acid reacts with dimethylaniline. Sometimes an excess of nitrite is taken.

4. Refer to 34.32.

5. It is better to calculate the approximate amount of acid that is needed. Most of this may be added quite rapidly to the amine.

6. Dimethylaniline tends to separate if the acidity diminishes too rapidly. The use of sodium acetate in place of sodium hydroxide has the advantage of buffering the solution without a rapid rise in pH.

7. Removal of soluble salts from the finely divided product is a long and tedious process. However, drying eliminates the colloidal properties, and filtration is much easier. The yield is essentially quantitative.

Questions

1. Why does the temperature of the solution drop below 0°?

2. How can one tell without using a thermometer that the temperature drops below 0°?

3. What is the reaction of nitrous acid with potassium iodide? Write the equation.

4. What is the reaction of nitrous acid with dimethylaniline?

5. Write the structure of sulfanilic acid; diazotized sulfanilic acid.

6. What is another name for diazotized sulfanilic acid? for methyl orange?

7. Which is more easily diazotized: aniline or sulfanilic acid?

8. What is meant by the invert method of diazotization?

9. When can the invert method be used?

10. What is meant by coupling?

11. With what types of compounds do diazo compounds couple?

Experiment 34-3　Preparation of Para Red (Note 1)

Prepare 0.02 mole of finely divided p-nitraniline hydrochloride as follows: Dilute an amount of c.p. hydrochloric acid (sp. gr. 1.18) containing *ca.* 0.1 mole of hydrogen chloride with an equal volume of water (Note 2). Dissolve 0.02 mole of p-nitraniline by heating with slightly more than 0.02 mole of the acid, adding additional small amounts of water and/or acid if necessary (Note 3). Add the rest of the hydrochloric acid, and cool the solution rapidly with agitation so as to obtain a loose mass of fine crystals, finally to 5° or lower.

Dissolve 0.03 mole of sodium nitrite in a small volume of water (5 or 6 ml.), and cool to 5° or lower by external cooling.

Add *ca.* 15 g. of clean dry finely crushed ice to the p-nitraniline hydrochloride and then all at once the sodium nitrite. Stir continuously until the solid dissolves. The temperature should rise to *ca.* 10°. Cool moderately if it rises to 15°. Let the mixture stand for 2 to 3 minutes at 10° to 15°, in order to complete the diazotization.

Dilute with cold water (50 to 75 ml.), filter if not clear, and pour the

diluted solution all at once and with vigorous stirring into a cold alkaline solution of β-naphthol (Note 4). This should be prepared shortly beforehand by dissolving 0.02 mole of β-naphthol in a solution of 0.04 to 0.06 mole of sodium hydroxide in *ca.* 400 ml. of water and *ca.* 0.05 mole of trisodium phosphate or sodium carbonate for buffering (Note 5). Stir vigorously for a few minutes, raise the temperature to *ca.* 30°, and stir continuously for 0.5 to 1 hour to aid coagulation (Note 6).

Collect the bright red solid by suction filtration (Note 7). After the solid has dried completely, extract the inorganic salt by stirring with water, collect again by suction filtration, wash until free of chloride ion, and wash with alcohol to remove organic impurities (refer to 5.42). Dry *completely* before weighing, and calculate the percentage yield (Note 8).

Notes

1. These directions serve, in general, as a guide for diazotizing amines, which are not so easily diazotized as aniline, and for the coupling of diazotized amines with phenols. If the coupling agent is an amine, instead of a phenol, it is added in the form of a hydrochloride salt. Following this, the *p*H is raised by the addition of a suitable buffering agent, for example sodium acetate, trisodium phosphate, sodium bicarbonate. The last has the disadvantage of evolving a gas. A neutral salt such as sodium chloride or sodium sulfate often is added for the purpose of salting out the product.

2. Technical hydrochloric acid can be used, although iron usually present is carried down with the product.

3. See 34.13 in regard to effect of excess acid on solubility.

4. Speed is important, because nitrous acid hastens the decomposition of the diazonium salt.

5. Trisodium phosphate has the advantage over sodium carbonate that coagulation may be aided by acidification without the evolution of a gas. The mixture during the coupling reaction should not become acidic; otherwise, nitrous acid may react with β-naphthol.

6. Coagulation is aided also by heating or by the addition of an electrolyte. Hydrochloric acid has the advantage of being volatile and thus is removed on drying. Salts present remain in the solid to some extent. If attempt is made to wash them out, the solid becomes more dispersed and the filtering more difficult. However, once the solid has been dried, extraction of the salts is easy.

7. Centrifuging avoids tedious filtering.

8. The yield is essentially quantitative.

Questions

1. Why is an excess of hydrochloric acid added?

2. Why not start the experiment with all the acid?

3. What do you believe is the reason for *p*-nitroaniline being more difficult than aniline to diazotize?

4. Why does the diazotization proceed better if the concentrations are high?

5. Why does the temperature of the mixture drop below 0°?

6. How can one tell, without using a thermometer, that the temperature drops below 0°?

7. Why is the nitrite added quickly?

8. Why is the solution of the diazonium salt added quickly to the β-naphthol?

9. Why is there no reaction between the excess nitrous acid and β-naphthol?

10. What is the approximate pH of the final reaction mixture?

11. What types of compounds couple with diazo compounds?

Experiment 34–4   Preparation of *p*-Aminoazobenzene

DIAZOAMINOBENZENE (Note 1). To 0.10 mole of dry *finely* ground sodium nitrite in a 500-ml. flask (Notes 2 and 3) add 0.6 mole of recently distilled aniline (Note 4). Cool to *ca.* 10° with outside cooling by means of ice or an ice–salt mixture, and while agitating *constantly* add drop by drop sufficient concentrated hydrochloric acid to furnish 0.13 mole of hydrogen chloride (Note 5). Maintain the temperature at 10 to 15° during the addition, which will require 15 to 20 minutes. Afterwards agitate constantly for *ca.* 5 minutes. A considerable amount of solid should have formed by this time. In order to complete the first step, heat to *ca.* 25° by means of a warm-water bath, and maintain at 25° to 30° for 5 or 10 minutes, swirling constantly.

REARRANGEMENT. Raise the temperature to 50° by means of a warm bath, and maintain at this temperature for *ca.* 1 hour. At first do not bother about any solid adhering to the upper part of the flask. Later, after the solid suspended in the organic phase has dissolved, close the flask with a tightly fitting stopper, and shake once or twice to wash down the solid. Repeat at intervals. Test for completeness of reaction (Note 6). If the reaction is not complete, let stand overnight.

ISOLATION OF THE FREE BASE. Purification of the product is facilitated by removal of most of the aniline first. In procedure 1 this is accomplished by steam distillation of aniline and in 2 by addition of hydrochloric acid, for *p*-aminoazobenzene is essentially nonvolatile with steam, and its hydrochloride is only slightly soluble in water. In case the directions of Note 2 are followed, purification according to procedure 1 is possible without steam distillation.

1. Add about 15 ml. of alcohol and about twice the amount of solid potassium hydroxide required to react with any amine hydrochloride remaining (Note 7). Boil gently under a reflux condenser for 2 to 4 minutes. Steam-distil (refer to Chapter 10) to remove most of the aniline. Let the contents cool without agitation so that a solid cake forms (Note 8). Pour off and discard the aqueous phase, rinse 2 or 3 times with water, and drain well.

Add 30 ml. of glacial acetic acid, dissolve by warming to 50° or 60°, filter through a small fluted filter into a small beaker, rinse out, and

wash with two or three small portions of warm glacial acetic acid (not over 10 ml. in all), and allow crystallization to proceed slowly. Let stand overnight, preferably (Note 9).

Collect the bright red needles by suction filtration on a small filter, pressing out well. Save the filtrate for a second crop. Wash the solid with glacial acetic acid from a dropper, using a minimum amount (note that, if suction is on, the wash liquid rushes through too rapidly). Dry *rapidly* and completely (Note 10).

Add water to the filtrate, 10 to 12 ml. (Note 11), warm to dissolve any precipitate, and allow to crystallize. Collect as before. Any wash liquid should have the composition of the mother liquor. If the solutions have been properly protected from the air, a third, reasonably pure crop may be obtained from the filtrate by cooling and/or by adding more water. Determine the melting points and yields of the respective crops (Note 12).

2. Add 150 to 200 ml. of warm water and then slowly, with continual agitation, sufficient concentrated hydrochloric acid to neutralize the bases present and furnish some excess (5 to 10%). Heat quickly to about 70° on a steam bath, and maintain at this temperature for 5 to 10 minutes, agitating frequently throughout (Note 13), so as to promote formation of steel-blue needles of *p*-aminoazobenzene hydrochloride. Allow to crystallize on cooling. Collect by suction filtration, and wash with water containing some hydrochloric acid until the aniline content of the filtrate is low (Notes 14 and 15).

In a suitable vessel and with thorough mixing decompose the salt by addition of a good excess of ammonium hydroxide. Be sure none of the salt remains (Note 16). Collect *p*-aminoazobenzene by suction filtration.

Purify by crystallization. In case this is done from acetic acid, the presence of moisture in the solid may require the use of a larger amount of acetic acid than in procedure 1. If benzene is the solvent (refer to 5.22), the solid preferably should be dried, but this is not necessary. However, if wet, the aqueous phase is sometimes difficult to remove. Try pouring the solution from one dry glass vessel to another. The solid crystallizes as yellow plates with 1 molecule of benzene. Calculate the percentage yield (Note 17).

Notes

1. *Caution:* Work with care so as not to spill any of the product or any of the solutions, since they leave stains. Do not dump any solutions into the sink, but pour them carefully down the drain opening. Thoroughly clean out apparatus, especially inside of funnels. Acetone works well.

2. The rearrangement proceeds more readily, the smaller the aqueous phase. This phase can be eliminated entirely by using aniline hydrochloride and an organic nitrite. Under these conditions a smaller excess of aniline can be taken. The amount specified below is about the minimum.

Add 0.05 to 0.10 mole of dry aniline hydrochloride to 0.4 mole of aniline. Heat to dissolve the solid, and cool quickly to about 30°. Add gradually 0.10 mole of n-butyl nitrite (Experiment 21-3) over a period of 15 to 20 minutes, mixing well. (*Caution: Hood:* Butyl nitrite is a powerful heart stimulant. Do not breathe the vapor.) Any aniline hydrochloride that crystallizes will dissolve as the butyl nitrite is added. Let the temperature rise spontaneously to 40° or 45°, and cool moderately if it goes higher or if decomposition sets in, as evidenced by gas evolution and foaming. Maintain at 40° to 50° under constant observation for about 10 minutes. Cool moderately if decomposition starts. From here on follow the directions under Rearrangement.

3. In case agitation is to be done manually according to Note 5, a conical flask is recommended. Since it is not desirable to make any more transfers than necessary, a 500-ml. flask is about the minimum.

4. The large excess of aniline is not needed for the reaction. It serves to dissolve water and thus to cut down the volume of the aqueous phase. When more water is present, the excess of aniline should be greater.

5. Agitation can be done conveniently by moving the bath back and forth, and the addition can be made from a dropper at the same time, using both hands, one for each operation.

6. Dissolve 1 drop in a few drops of glacial acetic acid and make a dilute (about 1%) solution of α-naphthylamine in glacial acetic acid. Apply a drop of each 1 cm. apart on filter paper. A violet color is produced a few seconds after contact if diazoaminobenzene is still present.

7. The alcohol increases the mutual solubility of the two phases and thus promotes reaction.

8. Formation of the cake facilitates removal of the aqueous phase without loss of organic material. In case steam distillation has been omitted or is incomplete, separation and washing of the organic phase can be done in a separatory funnel. However, purification of the product is more difficult.

9. There is a pronounced tendency to supersaturation in glacial acetic acid.

10. Use of a vacuum desiccator containing sodium hydroxide aids removal of last traces of acetic acid.

11. Water throws out impurities also; therefore, the amount should not be too large. More than 12 ml. probably can be added.

12. Yield: first crop 30%; second crop 40%. Melting points: first crop 122–123°; second crop 112–115°. The pure compound melts at 127°.

13. Prolonged heating of the hydrochloride in hydrochloric acid at the boiling temperature causes decomposition, with formation of p-phenylenediamine and other products.

14. Test for aniline hydrochloride by adding to a portion of the filtrate enough solid sodium hydroxide to make the solution alkaline. Note if aniline is present, as revealed by emulsion formation or by odor.

15. In case the hydrochloride is desired, this product may be dried; yield of somewhat impure product, 70%.

16. Grinding in a mortar with the ammonia solution (*Hood*) is desirable if the crystals of hydrochloride are not finely divided.

17. Yield, about 50%.

Questions

1. Why is the amount of hydrochloric acid not that specified in Experiment 34–1?

2. Why is the molal ratio of hydrochloric acid to sodium nitrite greater than unity?

3. Why is there such a large excess of aniline?

4. Why is it desirable to keep the amount of water a minimum?

5. What are the compounds present in the reaction mixture, after the 0.13 mole of hydrochloric acid has been added and rearrangement has taken place?

6. What are the amounts of these present (in moles), assuming that the reactions have taken place quantitatively?

7. What are the bases referred to?

8. What is the theoretical amount of hydrogen chloride (in moles) required to neutralize them?

9. To what volume of concentrated hydrochloric acid does this correspond?

10. Why not use aqueous sulfuric acid instead of hydrochloric acid?

11. Compare the solubility of *p*-aminoazobenzene hydrochloride in pure water with that in the actual reaction mixture.

12. What advantage does a hydrochloric acid wash have over one of pure water?

13. Explain why a large crystal of *p*-aminoazobenzene hydrochloride should be ground with aqueous ammonia.

14. What amount of base (in moles) is needed to react with any amine hydrochloride, after rearrangement?

15. Explain the difference between the following types of compounds: diazo, diazonium, diazotate, diazoamino, aminoazo.

Experiment 34–5   Preparation of Sudan III

DIAZOTIZING *p*-AMINOAZOBENZENE (Note 1). In a small conical flask (50 ml.) prepare a solution of 4.0 g. (0.02 mole) of *p*-aminoazobenzene (or an equivalent amount of the hydrochloride) in 20 to 25 g. of concentrated sulfuric acid (Note 2), heating to *ca.* 45° and agitating until most of the solid has dissolved, as judged by the fading out of especially dark spots on the glass. In another small flask prepare a solution of nitrosylsulfuric acid by adding 1.6 g. (0.023 mole) of *finely* powdered sodium nitrite (Note 3) to 20 g. of cold concentrated sulfuric acid, a little at a time, with cooling and agitation, finally heating to 40° or 45°, to effect complete solution of the nitrite. Separation of some sulfate does not matter.

Add the warm nitrosylsulfuric acid in small portions to the other warm solution (*ca.* 40°), agitating well. In case evolution of gas takes place, cool slightly (Note 4). Rinse out the flask with 2 or 3 g. of concentrated sulfuric acid, and add it also. Let stand warm for 15 to 30 minutes, agitating at intervals. In the meantime prepare the materials below, and, when they are ready, pour the reaction mixture onto *clean* crushed ice with stirring in a large (1000-ml.) beaker, adding more ice if the temperature rises above 0°.

COUPLING WITH β-NAPHTHOL. In a conical flask dissolve 2.9 g. (0.02 mole) of β-naphthol in *ca.* 400 ml. of pure water (Note 5) containing 0.05 to 0.1 mole of sodium hydroxide. Weigh out an amount of powdered sodium acetate (Note 6) that is in excess (*ca.* 5%) over the amount necessary to convert the mineral acid (or acids) to acetic acid. Add enough *clean* crushed ice to bring the volume of the diazonium solution to 300 or 350 ml., and without delay add the sodium acetate in a stream with *vigorous* agitation so as to prevent caking and then the solution of β-naphthol slowly in a *very fine stream with vigorous agitation*.

Remove the ice so that the temperature will rise, and stir mechanically for *ca.* 0.5 hour to facilitate coupling by dissolving the sparingly soluble reactants, namely, β-naphthol and the diazonium sulfate. Stirring also aids coagulation of the dye. Collect on a Buechner funnel, wash with dilute hydrochloric acid (1 *N* or 2 *N*; Note 7) to remove sulfate ion completely, and wash twice with alcohol to remove any β-naphthol. Dry thoroughly, and calculate the percentage yield (Notes 8 and 9).

Notes

1. The salts of *p*-aminoazobenzene are sparingly soluble in water. Partly because of this fact and partly because aminoazobenzene is a weaker base than aniline, the diazotization with aqueous nitrous acid is quite slow. The procedure here described

can be followed for the diazotization of other bases which are difficult to diazotize, for example 2,4-dinitroaniline, 2,4-dichloroaniline, and aminopyridines.

2. Keep a record of the amount of sulfuric acid. Try to keep this amount as small as possible. The amount of sodium acetate added later depends on the amount of sulfuric acid. In case the hydrochloride of p-aminoazobenzene is taken, do the heating in the hood since hydrogen chloride is evolved.

3. Note that sodium nitrite usually is not 100% pure. More complete diazotization is realized if there is an excess ($ca.$ 10%). In case an excess is taken, add a small amount of urea ($ca.$ 1 g.) after diazotization is complete, and let stand warm for 5 to 10 minutes afterward, to allow time for the excess to decompose. There is some evidence that the diazotization reaction is reversed by urea in sulfuric acid.

4. Observe the surface for gas evolution by looking down into the flask. Good illumination is necessary.

5. A high dilution is desirable so that the solid β-naphthol, as it is thrown out of solution on contact with the diazonium solution, will be in a finely divided form. Since the solution slowly darkens on exposure to air, it should be made immediately preceding use and preferably in a flask.

6. Anhydrous sodium acetate dissolves with evolution of heat; the dihydrate with absorption of heat. The anhydrous, if finely divided, dissolves quite readily when added to the diazonium solution but is liable to cake if the stirring is not vigorous.

7. The product is less liable to be peptized if the wash water contains an electrolyte.

8. In case small light-colored particles are visible or the weight is too great after thorough drying, grind the product to a fine powder, stir with considerable dilute hydrochloric acid, filter as before, and dry.

9. The yield is essentially quantitative.

Questions

1. Explain why p-aminoazobenzene is a weaker base than aniline.

2. Why are aromatic amines which are weaker bases than aniline more difficult to diazotize?

3. Why can such amines be diazotized more easily by nitrosylsulfuric acid?

4. Why is diazotization liable to be more complete if there is an excess of sodium nitrite?

5. Which is more stable: nitrous acid or nitrosylsulfuric acid?

6. What other methods are useful for diazotizing aromatic amines?

7. Why does β-naphthol separate when its solution in dilute sodium hydroxide is added to the diazonium solution?

8. Why is it desirable that it separate in a finely divided form?

9. Explain the different heat effects when water is added to anhydrous and to hydrated sodium acetate.

10. Why not use aqueous sodium chloride instead of hydrochloric acid as wash water?

11. What three main types of compounds are obtained from diazonium compounds by coupling?

12. Under what conditions does coupling take place?

Chapter 35

AROMATIC HYDROXY COMPOUNDS

SECTION 35.1   ALCOHOLS

Aromatic alcohols may be prepared by several of the general methods used for aliphatic alcohols in Chapter 19.   The hydration of aromatic olefins (method a, Chapter 19) seldom is used.   Hydrolysis of the halide (method b) is excellent for converting a benzyl halide to a benzyl alcohol, but, if the halogen atom is attached to a secondary or tertiary carbon atom, a strong base usually yields mainly the unsaturated compound.   The saponification of esters (method c) is not of importance, for the esters usually are prepared from the alcohols, since few aromatic alcohols occur naturally as esters.   The hydrogenation of aldehydes and ketones (method e) and of esters (method f) usually gives low yields, owing to the tendency of these aromatic compounds to be reduced further to a hydrocarbon.   Benzyl alcohol undergoes hydrogenolysis to toluene.   Of the methods discussed in Chapter 19, reduction of aldehydes and ketones by aluminum isopropoxide (method g) and the use of the Grignard reagents (method d) probably are best for preparing aromatic alcohols other than benzyl alcohol.   In addition to the methods discussed in Chapter 19, primary aromatic alcohols in which the CH_2OH group is attached to the benzene ring are obtained conveniently from the corresponding aldehydes by dismutation in the Cannizzaro reaction (method j):

(j) $\qquad$ $2C_6H_5CHO + NaOH \rightarrow C_6H_5CH_2OH + C_6H_5COONa$

$\qquad$ $HCHO + C_6H_5CHO + NaOH \rightarrow C_6H_5CH_2OH + HCOONa$
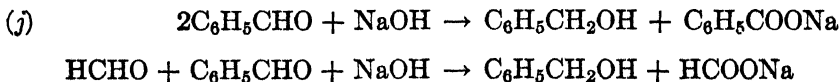
35.11   The Cannizzaro Reaction.   In method j reaction takes place when benzaldehyde or a substituted benzaldehyde is shaken with a concentrated aqueous sodium or potassium hydroxide solution at room temperature.   This reaction has the disadvantage of being limited to a 50% yield.   This may be circumvented by the use of formaldehyde as the reducing agent.   With an excess of formaldehyde, yields of alcohols of the order of 90% may be realized.   A side reaction is the oxida-

tion of the aromatic aldehyde to the acid. This takes place to the extent of about 5%. Of course, aldehydes having *alpha* hydrogen atoms cannot be used, since they undergo the aldol condensation. Formaldehyde has the advantages that it and its products of dismutation can be removed by water and also that it is inexpensive. Benzyl alcohol (Experiment 35–1) is prepared from benzaldehyde by this method.

35.12 Thermochemistry. When the calculation of the gas-phase dismutation of benzaldehyde with water to benzoic acid and benzyl alcohol is made from bond energies and resonance energies, the reaction is exothermic to the extent of 15 kcal. The calculated value for the liquid-phase reaction is about 5 kcal., it being assumed that the heats of vaporization of the organic compounds are about the same. However, the heat of neutralization of the acid by the sodium hydroxide causes the over-all reaction to be decidedly exothermic.

35.13 Side Reactions. The side reaction that may cause the yield of a carbinol to be low is loss of water to form a double bond. Of course, this is possible only when the side chain has two or more carbon atoms. Many primary and secondary alcohols can be distilled at atmospheric pressure without decomposition, but tertiary alcohols, for example dimethylphenylcarbinol, decompose slowly when distilled. The dehydration reaction is catalyzed by acids (see Chapter 19); thus distillation of a secondary or tertiary carbinol in contact with a suitable substance (phosphoric acid, potassium bisulfate, etc.) converts it largely to the corresponding olefinic compound. The decomposition is facilitated if the double bond is conjugated with the benzene ring, that is, is attached to the α-carbon atom.

The presence of any acidic substance in the reaction product obtained by any of the methods mentioned is hardly likely, since the reaction mixtures are neutral or basic. However, if sulfuric acid is used in the decomposition of a Grignard reaction product (method *d*) care must be taken to remove it completely from the ether solution before evaporation of the solvent. Distillation at reduced pressure is necessary with tertiary alcohols and usually is worth while with secondary alcohols.

<div align="center">SECTION 35.2 PHENOLS</div>

Phenols are prepared by: (*a*) the fusion of sulfonic acids with caustic alkali, (*b*) high-temperature treatment of aryl halides with caustic alkali, (*c*) the scission of alkyl–aryl ethers, by heating with hydrobromic or hydriodic acid, (*d*) heating diazonium salts with water, (*e*) decarboxylation of phenolic carboxylic acids, (*f*) condensation of alcohols

with phenols, (*g*) rearrangement of phenyl esters to ketonic phenols, which can be reduced (see Clemmensen reduction, 29.17).

(*a*) $2KOH + C_6H_5SO_3K \longrightarrow C_6H_5OK + K_2SO_3 + H_2O$

(*b*) $2NaOH + C_6H_5Cl \longrightarrow C_6H_5ONa + NaCl + H_2O$

(*c*) $HBr + C_6H_5OCH_3 \longrightarrow C_6H_5OH + CH_3Br$

(*d*) $NaNO_2 + 2H_2SO_4 + C_6H_5NH_2 \longrightarrow$

$$C_6H_5N_2SO_4H + NaHSO_4 + 2H_2O$$

$HOH + C_6H_5N_2SO_4H \longrightarrow C_6H_5OH + N_2 + H_2SO_4$

(*e*) $C_6H_2COOH(OH)_3\text{-}2,4,6 \longrightarrow C_6H_3(OH)_3\text{-}1,3,5 + CO_2$

(*f*) $(CH_3)_3COH + C_6H_5OH \xrightarrow{\text{ZnCl}_2} (CH_3)_3C{-}C_6H_4{-}OH + H_2O$

(*g*) $C_6H_5{-}O{-}COC_5H_{11} \xrightarrow{\text{AlCl}_3} o\text{-}C_5H_{11}CO{-}C_6H_4OH$

$4HCl + 2Zn + C_5H_{11}COC_6H_4OH \longrightarrow$

$$C_5H_{11}CH_2C_6H_4OH + 2ZnCl_2 + H_2O$$
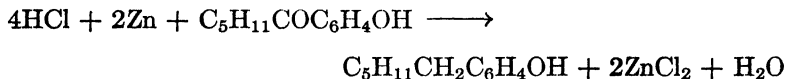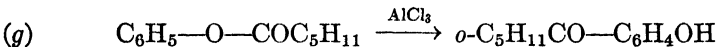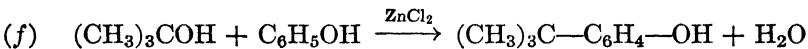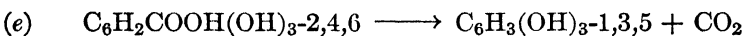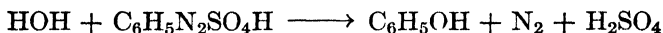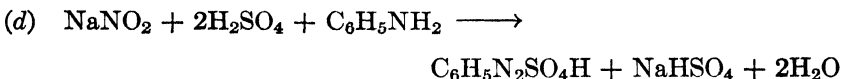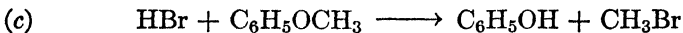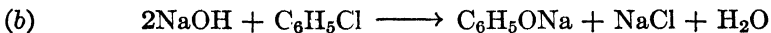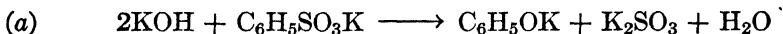
In method *a* the reaction is carried out at 250° to 300°. Often potassium hydroxide will give much better yields than sodium hydroxide. The yields in ordinary laboratory practice usually are not good, owing in part to side reactions, mainly oxidation, although industrially the method is satisfactory because temperature control is better. Likewise method *b* is an important industrial operation where the high temperatures required are obtained by working under pressure. Method *c* may be used for preparing phenols from naturally occurring ethers such as vanillin or safrole. Scission may be accomplished by refluxing with concentrated hydroiodic acid or by heating in a sealed tube with a saturated solution of hydrogen bromide in glacial acetic acid.

35.21 Decomposition of Diazonium Salts. Method *d* probably is one of the most useful for laboratory work since amines are readily available by the reduction of nitro compounds (see Chapter 33). In Experiment 35–2 phenol is prepared from aniline in this way. In method *e* decarboxylation is aided by the presence of hydroxyl groups in positions *ortho* or *para* to the carboxyl group. Thus 2,4-dihydroxy- and 2,4,6-trihydroxybenzoic acids lose carbon dioxide when an aqueous solution is boiled. Salicylic and *p*-hydroxybenzoic acids require higher temperatures and decompose at their melting points, while *m*-hydroxybenzoic acid is stable.

35.22 Condensation of Alcohols with Phenols. In method *f* reaction may take place in the presence of anhydrous aluminum chloride

or zinc chloride. Generally, tertiary alcohols condense more readily than secondary, and these more readily than primary. Aluminum chloride is a more effective catalyst than zinc chloride. In contact with aluminum chloride, phenol reacts with tertiary butyl alcohol at 25° to 30°, with sec-butyl alcohol at 120° to 140°, and with n-butyl alcohol at a little higher temperature. The yields are 50 to 70%. In contact with zinc chloride phenol reacts with isobutyl alcohol at 180° as in Experiment 35–3.

35.23 Rearrangement of Phenyl Esters. In method g reaction is carried out by heating the ester with a suitable catalyst, for example anhydrous aluminum, iron, or zinc chloride, to a temperature of ca. 140°. The product is both a phenol and a ketone. Amalgamated zinc and hot hydrochloric acid reduces the ketonic side chain to an alkyl side chain (Clemmensen method) and thus yields the alkyl phenol.

Experiment 35–1   Preparation of Benzyl Alcohol (Note 1)

Mix 0.10 mole of freshly distilled benzaldehyde (Note 2), a 40% excess of formaldehyde (Note 3), and 40 ml. of methanol (Note 4) in a flask (Note 5). Stopper the flask to prevent ready access of air, and cool the contents to about 5°. Add 0.3 mole of potassium hydroxide in several portions, shaking continuously until dissolved. Keep the flask stoppered and the liquid cold (Note 6). Let stand cold for about 0.5 hour. Attach a condenser, and distil until essentially all methanol has been removed, taking care not to lose benzyl alcohol by steam distillation.

Transfer cold to a separatory funnel with 50 to 100 ml. of water, and extract three or four times with 15- to 25-ml. portions of benzene each time (Note 7). Save the aqueous phase. Remove methanol from the benzene phase by two or three shakings with water, and dry with a suitable drying agent (Note 8). Distil from a flask which is suitable for a small amount of high-boiling liquid, taking cuts if intermediate fractions are significant, and redistilling in systematic fashion (refer to Subsection 9.13). Collect over a reasonable range (Note 9), and calculate the percentage yield. Recover the benzoic acid formed in the side reaction, and calculate the benzaldehyde accounted for.

Notes

1. This procedure may be used for the reduction of many substituted benzaldehydes to the corresponding alcohols if the substituent is not easily reduced and is unreactive under the alkaline conditions, as for example halogen, alkyl, and alkoxy groups.

2. On exposure to air, benzaldehyde is oxidized rapidly to benzoic acid. It should be redistilled before use, if it has been kept in a glass-stoppered bottle.

3. Formalin solution is 35 to 40% formaldehyde.

4. This amount should be increased until there is only one liquid phase, in case two liquid phases form when the potassium hydroxide is added later.

5. If a Kjeldahl flask is available the operations can be simplified, for it will not then be necessary to stopper the flask, and the methanol can be boiled out (*Hood*).

6. Autooxidation of benzaldehyde is more rapid, the higher the temperature. The yield is usually lower if the reaction mixture is not cooled.

7. Sometimes potassium benzoate is extracted by benzene if much methanol remains.

8. Refer to Chapter 12, Tables 12-2 and 12-3.

9. The boiling point of benzyl alcohol is 205°; yield, 80%.

Questions

1. Why should there not be two liquid phases?
2. Why should the flask be kept stoppered?
3. Why is it desirable to distil over most of the methanol before adding water?
4. What happens to part of the potassium hydroxide?
5. Why is water added before extracting with benzene?
6. What drying agents are suitable?
7. What other extracting solvents are satisfactory?
8. How can the formation of benzoic acid be minimized?
9. What is the main impurity in the final product?
10. How can this be removed?

Experiment 35–2   Preparation of Phenol from Aniline

Mix 200 ml. of water, 0.5 mole of concentrated sulfuric acid, and 0.20 mole of aniline (not dark colored). Heat if necessary, to effect solution, and then cool rapidly with agitation, to obtain a fine-crystal meal. Add about 100 g. of ice and then a solution of an equivalent amount of sodium nitrite (Note 1) in 80 to 100 ml. of water. The first three quarters or four fifths may be added rapidly with stirring. After that add small portions until a well-marked positive test for excess nitrous acid is obtained (Note 1). Add more ice if the temperature rises above 5°.

Set up an apparatus for steam distillation with a flask not smaller than 1 liter (refer to Chapter 10). Transfer the solution to this, and heat slowly to about 50°, or let stand overnight (Note 2). Distil with steam until the initial two-phase distillate becomes a one-phase distillate. Continue collecting until about 100 ml. of the subsequent one-phase distillate comes over (see Question 5). About half-saturate the distillate with sodium chloride or other readily soluble inorganic salt,

and extract about three times with ether (Note 3). Dry the ether extract with anhydrous magnesium sulfate, and allow the ether solution to run slowly into a small distilling flask as the ether is being distilled off through a long condenser (Note 4) while heating with warm water. After the ether is removed, heat with a flame, and above 150° use the side arm as a condenser (Note 5), distilling *slowly* (Note 6) and collecting a 5° fraction near 180°. (*Caution:* Note 7.) Calculate the percentage yield (Note 8).

Notes

1. Refer to 34.13.
2. The reaction is exothermic. If the mixture is heated too rapidly, foaming may become excessive. Some of the phenol couples with the diazonium compound. This side reaction can be diminished by dilution, by increasing the acid concentration or by removing the phenol as it is formed. The last can be done by running the cold diazonium solution slowly into boiling dilute sulfuric acid (about 10%) and steam-distilling the phenol as it is formed.
3. Isopropyl ether may be used although the phenol thus obtained is not so pure, probably owing to the presence of peroxide in the ether.
4. Take the usual precautions when distilling ethyl ether.
5. The side arm should be at least 20 cm. long if it is to act as a condenser.
6. The phenol should not have a high vapor pressure as it leaves the apparatus.
7. Phenol is a poison. The vapors should not be breathed. The liquid should not come in contact with the skin, because it produces burns that are slow to heal. The skin should be washed *at once* with alcohol. The application of camphor also affords relief. Phenol is absorbed through the skin from dilute aqueous solutions without the production of burns, but sometimes with bad physiological effects.
8. Yield is 50 to 60%.

Questions

1. Why is the molal ratio of sulfuric acid to aniline not 2 to 1, according to the equation?
2. Why must the solution be kept cold?
3. Why not use hydrochloric acid in place of sulfuric acid?
4. Explain how dilution, or increasing the concentration of sulfuric acid, could increase the yield.
5. What is the minimum amount of water required to steam-distil the theoretical yield of phenol, assuming it is insoluble in water?
6. Name other satisfactory drying agents for an ether solution of phenol.
7. Why is salt added to the aqueous phase?
8. Give another reaction used in the preparation of phenol.
9. Are the aromatic diazo compounds important? Explain.
10. Write the structure of a diazonium salt.
11. What types of compounds may be prepared by replacement of the diazonium group?
12. What are the probable impurities in the crude and final products?
13. What steps have been taken to remove them?

Experiment 35–3   Preparation of *p-tert*-Butylphenol

In a 2-necked round-bottomed flask of 200 or 300 ml. capacity to which is attached a thermometer with bulb reaching to the bottom and a reflux condenser, place 0.2 moles of crystalline phenol, 0.4 mole of anhydrous zinc chloride (Notes 1 and 2), a few drops of concentrated hydrochloric acid (Note 3) and 0.2 mole of isobutyl alcohol (Notes 4 and 5). Mix the contents with a swirling motion, and heat with a small flame, with frequent agitation to promote solution of the zinc chloride (Note 6). After the zinc chloride has dissolved, reflux the mixture for a period varying from $\frac{1}{4}$ to 2 hours, depending on whether or not the reaction mixture changes (Notes 7 and 8). Maintain the temperature of the mixture above 180°, if possible. Keep a chronological record of all variable factors, so that the time to stop heating can be determined by inspection of the data.

Cool, add water, and extract the organic compounds twice with benzene (*ca.* 25 to 50 ml.). Wash a few times with water. Distil the mixture, replacing the water-jacketed condenser with an air condenser, and drying the apparatus, when the distilling temperature rises to 150° (*Hood*). Distil slowly until phenol is removed, and then collect fractions up to about 250°. Redistil the cuts slowly in systematic fashion (refer to 9.13), collecting a 5° fraction near the boiling point of *p-tert*-butylphenol, repeating if neighboring fractions are large in amount (Notes 9 and 10). Crystallize the product from low-boiling ligroin. Label product with boiling point and melting point, and calculate the yield of crude and crystallized products.

Notes

1. Temperature to which the reaction mixture can be raised depends on the ratio of zinc chloride to alcohol. When this is 2, a satisfactory reaction rate is realized. Zinc chloride catalyzes the condensation reaction, partly by virtue of the high temperature of the mixture. However, it catalyzes unsaturation also.

2. Technical zinc chloride powder is satisfactory.

3. The reaction has been observed to proceed more rapidly when a small amount of hydrochloric acid is added.

4. When tertiary butyl alcohol replaces isobutyl alcohol, reaction is more rapid, and here also the product is *tert*-butylphenol. The reaction should be carried out at a lower temperature, however, since unsaturation takes place more easily. A study of the effect of conditions on yields is a worth-while problem for the better students.

5. An excess of the alcohol is no advantage unless some is lost by dehydration to butene. A large excess may be disadvantageous in cutting down the reaction temperature.

6. So long as solid is present, the heating should be done carefully. Also olefin formation is greater if zinc chloride is not dissolved.

7. One observer has noted that the crude yield is 55% at 15 minutes, and 45% at 60 minutes. This point needs further investigating. Others have heated for longer periods of time, with yields of crude and crystallized product of 80 and 45%, respectively.

8. The reaction mixture should separate into two liquid phases after about 15 minutes refluxing. Note the temperature readings as the reaction proceeds.

9. The *ortho* isomer is a liquid distilling at about 230°.

10. Pure *p-tert*-butylphenol distils at 238–239° at 737 mm., and melts at 98.5°. It sublimes as long hairlike shining needles at temperatures near 100°. It is said to be a good antiseptic. Yield of solid (m.p. 95–8°), 20%.

Questions

1. What other substances catalyze this reaction?

2. What would be the main reaction product in case the amount of alcohol was doubled and the time of heating extended?

3. What structurally is the difference between a phenol and an aromatic alcohol?

4. What product do you predict would be obtained if benzyl alcohol replaces isobutyl alcohol?

5. What product or products do you predict would be formed by the action of 1 and of 2 moles of bromine on 1 mole of *tert*-butylphenol?

6. What is the main impurity in the crude product?

7. What steps were taken to remove it?

Experiment 35–4   Properties of Phenols and Alcohols

A   SOLUBILITY.   To about 5 g. of solid phenol add a *few* drops of water. Note any change. After the mixture becomes homogeneous (warm if necessary), place equal amounts in three flasks, and while agitating add (*a*) water, (*b*) 3 N sodium carbonate, and (*c*) 3 N sodium hydroxide, respectively, until dissolved. Note the volumes required. Save the water solution for tests below.

B   COLOR TEST WITH FERRIC CHLORIDE.   To about 5 ml. of the aqueous phenol solution add a few drops of aqueous ferric chloride; compare with addition to pure water. Repeat the ferric chloride test with very dilute aqueous solutions of resorcinol, α-naphthol, benzyl alcohol, and ethyl acetoacetate, taking about 0.1 g. of the solid, or 1 drop of the liquid, in about 5 ml. of water (Note 1).

C   BROMINATION.   To the aqueous solution of phenol add bromine water to slight yellow color. Compare with the action of bromine water on aqueous solutions of aniline, benzoic acid, ethyl acetoacetate, and benzyl alcohol.

D   ACTION OF SULFURIC ACID.   To a small amount of phenol (*ca.* 1 g.) in a test tube add two or three times its weight of concentrated sulfuric acid. Keep at a temperature of 70° to 100° for 10 or 15 minutes. Cool,

add ice, two to three times the weight of the acid. Note if phenol separates.

Repeat with benzyl alcohol, in place of phenol.

E CONDENSATION TO A PHTHALEIN. To a mixture of about 0.2 g. of phthalic anhydride and about 0.1 g. of phenol add a small drop of concentrated sulfuric acid. Heat in an oil bath at about 150° for about 5 minutes. Cool, and digest the reaction mixture with boiling water. Make the aqueous extract alkaline. Repeat, with α-naphthol and with resorcinol replacing phenol.

Notes

1. The color obtained with ethyl acetoacetate is due to the presence of some of the enol form $CH_3C(OH){=}CHCOOC_2H_5$.

Questions

1. Why does phenol liquefy when water is added to the extent of only 3 to 5%?

2. Explain the behavior of phenol with sodium carbonate and sodium hydroxide solutions.

3. What is formed when bromine water is added to an aqueous solution of phenol?

4. What is formed when an excess of bromine water is added? Equation.

5. Compare the ease of bromination of phenol with the bromination of benzene, p-nitrotoluene, and aniline.

6. Write the equations for the condensation reactions.

7. Write the structural formulas of the compounds actually responsible for the intense colors in E.

8. Explain the difference in behavior of phenol and benzyl alcohol in B, C, and D.

9. Point out any similarity in the structure of phenol and the enol form of acetoacetic ester.

Chapter 36

AROMATIC ALDEHYDES AND KETONES

In addition to the methods described in Chapter 25, aromatic aldehydes may be obtained by: (a) oxidation of benzyl chloride (or a ring-substituted derivative), and (b) condensation of chloroform with a phenol (Reimer–Tiemann method for phenolic aldehydes). Aromatic aldehydes and ketones may be prepared by: (c) hydrolysis of α,α-dihalogen compounds, (d) oxidation of side chains, (e) condensation of a phenol with hydrogen cyanide or with a nitrile by means of hydrogen chloride (Gattermann synthesis), and (f) condensation with acid chlorides or acid anhydrides (Friedel–Crafts reaction).

(a) $2C_6H_5CH_2Cl + Cu(NO_3)_2 \longrightarrow$

$$2C_6H_5CHO + CuCl_2 + H_2O + NO + NO_2$$

(b) $C_6H_5OH + CHCl_3 + 4NaOH \longrightarrow$

$$NaOC_6H_4CHO + 3NaCl + 3H_2O$$

$$NaOC_6H_4CHO + HCl \longrightarrow HOC_6H_4CHO + NaCl$$

(c) $C_6H_5CHCl_2 + K_2CO_3 \xrightarrow{H_2O} C_6H_5CHO + 2KCl + CO_2$

(d) $3p\text{-}NO_2C_6H_4CH_3 + 4CrO_3 + 12Ac_2O \longrightarrow$

$$3p\text{-}NO_2C_6H_4CH(OAc)_2 + 4Cr(OAc)_3 + 6AcOH$$

$$p\text{-}NO_2C_6H_4CH(OAc)_2 + H_2O \longrightarrow p\text{-}NO_2C_6H_4CHO + 2AcOH$$

(e) $C_6H_5OH + HCl + HCN \longrightarrow HOC_6H_4CH{=}NH \cdot HCl$
    p-hydroxybenzaldimine hydrochloride

$$HOC_6H_4CH{=}NH \cdot HCl + H_2O \longrightarrow HOC_6H_4CHO + NH_4Cl$$
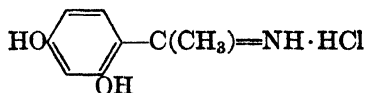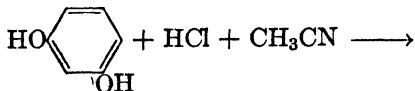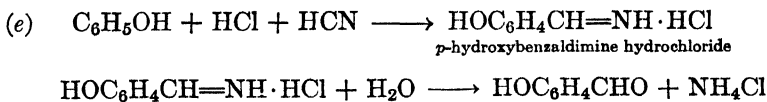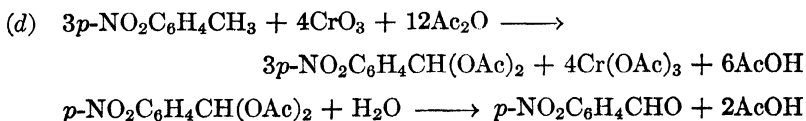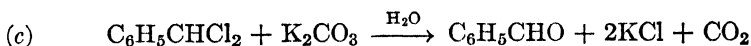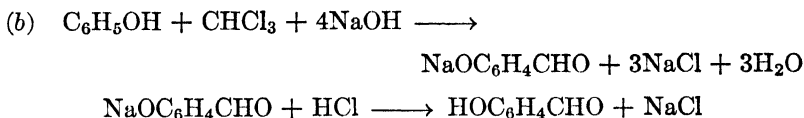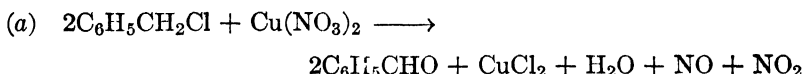
methyl-2,4-dihydroxyphenyl ketimine hydrochloride

$$HO-C_6H_3(OH)-C(CH_3)=NH \cdot HCl + H_2O \longrightarrow$$

$$HO-C_6H_3(OH)-COCH_3 + NH_4Cl$$

(f) $CH_3COCl + C_6H_6 + AlCl_3 \xrightarrow{AlCl_3} CH_3COC_6H_5 \cdot AlCl_3 + HCl$

$COCl_2 + 2C_6H_6 + AlCl_3 \xrightarrow{AlCl_3} C_6H_5COC_6H_5 \cdot AlCl_3 + 2HCl$

$(CH_3CO)_2O + 2C_6H_6 + 3AlCl_3 \xrightarrow{AlCl_3}$

$$2CH_3COC_6H_5 \cdot AlCl_3 + AlOCl + 2HCl$$

$CO + HCl + CH_3C_6H_5 \xrightarrow[CuCl]{AlCl_3} 1,4\text{-}CH_3C_6H_4CHO + HCl$
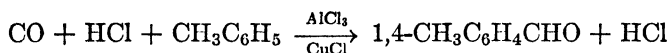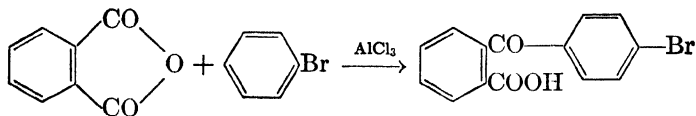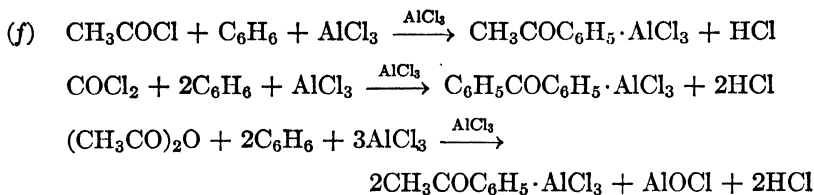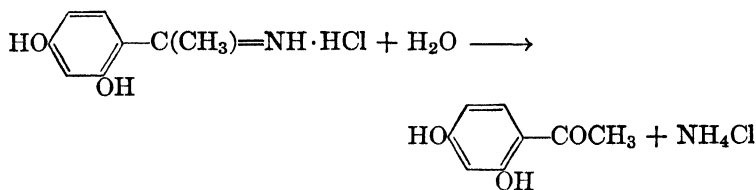
36.11   Oxidation of Benzyl Chloride. In method *a* benzyl chloride and some ring-substituted derivatives undergo a combined hydrolysis and mild oxidation when heated with aqueous lead nitrate or copper nitrate. The course of the reaction can be followed by the evolution of oxides of nitrogen.

36.12   The Reimer–Tiemann Condensation. Method *b* is carried out by adding chloroform gradually to a warm solution of the phenol in aqueous sodium hydroxide. For the gas-phase reaction of a phenol, chloroform, and water to give the aldehyde and hydrogen chloride, ΔH is -12.5 kcal. from bond-energy calculations. For the aqueous-phase reaction in the presence of sodium hydroxide, ΔH is then of the order of -20 kcal. The reaction therefore is quite exothermic. The reaction mixture will warm itself quite rapidly, especially if alcohol is added to give a single-phase system. This method yields a mixture of the *ortho* and *para* isomers. When hydrochloric acid is added, the product separates. In some cases such as the hydroxybenzaldehydes, the *ortho* isomer distils with steam and in this way can be separated from the *para* isomer. A side reaction is the Cannizzaro reaction of the aldehyde in the basic solution.

36.13   Hydrolysis of α,α-Dihalogen Compounds. In method *c* hydrolysis is effected by heating with aqueous carbonate or acid. Strongly alkaline media are not desirable because of the dismutation

reaction (Chapter 35, method h). Benzal chloride or a ring-substituted benzal chloride yields an aldehyde, whereas a disubstituted methylene chloride yields a ketone.

36.14 Oxidation of Side Chains. In method d alkyl side chains may be oxidized by different means. When chromyl chloride is used, it is added to the hydrocarbon in chloroform solution, and the precipitated addition product is cautiously decomposed by the addition of water. Methyl side chains are converted to CHO. Ethyl benzene yields a mixture of phenylacetaldehyde and acetophenone. Methyl side chains may be oxidized to CHO by chromic anhydride in a cold mixture of glacial acetic acid, acetic anhydride, and concentrated sulfuric acid. The aldehyde diacetate is formed and separates when water is added. Hydrolysis by dilute aqueous acid yields the aldehyde. Other oxidizing agents which have been used for oxidizing CH_3 to CHO are manganese dioxide, sulfuric acid and water; lead peroxide and sulfuric acid; persulfate and silver nitrate.

36.15 The Gattermann Synthesis. In method e the phenol and an excess of anhydrous hydrogen cyanide are dissolved in dry benzene or dry ether. A condensing agent such as anhydrous aluminum chloride or zinc chloride is added, and anhydrous hydrogen chloride is passed through the mixture with slight warming. The formation of the aldimine hydrochloride usually is complete in a few hours. The aldehyde is formed when the reaction mixture is decomposed with acidified water.

The aldehyde group enters the molecule *para* to the hydroxyl group. If that position is blocked, it enters in the *ortho* position. When two reinforcing hydroxy groups are present as in resorcinol, the reaction will take place without a condensing agent.

Ketones can be prepared from nitriles and the more reactive phenols, for example, resorcinol, in a similar manner. Phenol ethers also can undergo these reactions.

36.16 The Friedel–Crafts Synthesis. Method f, which is discussed in Chapter 29, is more widely used than any other method for the preparation of ketones and is even used for aldehydes. Ketone reagents are acid chlorides, acid anhydrides, the acids themselves, and phosgene. Aldehydes may be prepared using carbon monoxide and hydrogen chloride. More aluminum chloride is needed than in the hydrocarbon synthesis, owing to the fact that the ketone forms an addition compound with the aluminum chloride. Thus with acid chlorides more than 1 mole of $AlCl_3$ per mole of acid chloride is desirable, preferably about 2. With acids, at least 2 moles are required, since 1 mole reacts with the acid, when heated, to give the acid chloride. Preferably there should be at least 2.5 moles.

$$CH_3COOH + AlCl_3 \longrightarrow CH_3COOH \cdot AlCl_3$$

$$CH_3COOH \cdot AlCl_3 \xrightarrow{\text{heat}} CH_3COCl + HCl + AlOCl$$

With acid anhydrides at least 3 moles are required, preferably 3.5 moles, to utilize both acyl groups of the anhydride, according to the equation in f. If only 2 moles of aluminum chloride are added, only one acyl group is utilized. The reaction is slower than with acid chlorides, and longer heating is necessary.

Hydrocarbons undergo the reaction readily, the acyl group taking up a position *para* to the side chain. Other *ortho–para*-directive radicals on the benzene ring promote condensation, as for example halogen atoms, ether groups, and acylamino groups, but phenols often do not react satisfactorily. However, resorcinol and hexoyl chloride yield a dihydroxy phenyl amyl ketone, which on reduction by the Clemmensen method is converted into hexylresorcinol. The methyl group of a methyl ether is removed unless the reaction mixture is kept cold. The position taken by the acyl radical is *para* to an o,p-directing group. If the *para* position is occupied, the acyl group may enter the *ortho* position, but more slowly.

A *meta*-directing radical so retards the reaction that no condensation takes place unless also a strongly activating group is present. Therefore, as a rule only one acyl group can be attached to the benzene ring by the Friedel–Crafts reaction. Nitrobenzene does not react. It sometimes serves as a solvent in Friedel–Crafts syntheses.

The synthesis of aldehydes with carbon monoxide in the presence of aluminum chloride and hydrogen chloride presumably involves the formation of formyl chloride, ClCHO, which condenses with the hydrocarbon. Benzene homologs undergo the reaction readily and the aldehyde group enters the *para* position. The reaction with benzene is negligible under ordinary conditions but proceeds better when heated or when aluminum bromide is used in place of the chloride.

Symmetrical aromatic ketones may be prepared with phosgene or with carbon tetrachloride. With the latter (in excess), a dichloride is first formed, and this when hydrolyzed (method c), yields the ketone.

An important extension of the Friedel–Crafts reaction is the use of phthalic anhydride, which yields o-benzoylbenzoic acid, or a derivative, as in Experiment 36–2. A side reaction is the formation of a phthalide, which becomes the main reaction at a higher temperature (refer to 39.12). Benzoylbenzoic acids can be converted into anthraquinone compounds by heating with sulfuric acid (refer to 38.14).

Experiment 36–1   Preparation of Acetophenone

In a three-necked flask provided with a dropping funnel, a mechanical stirrer (Note 1), and a reflux condenser connected to a device which allows the hydrogen chloride to be absorbed without danger of sucking back (Note 2), place 0.7 to 1.0 mole of pure anhydrous benzene (Notes 3 and 4) and 0.4 mole of anhydrous aluminum chloride (as AlCl$_3$; Note 5). Allow to run in slowly through the dropping funnel, with agitation and over a period of 0.5 to 1 hour, 0.2 mole of recently distilled acetyl chloride or acetic anhydride (Notes 6 and 7). After reaction slackens, heat for about 1 hour at 90° to 100° by means of a bath (Note 8).

Cool, and pour the reaction mixture, with vigorous stirring, into a mixture of about 100 ml. of 6 N hydrochloric acid and 100 g. of ice in a beaker (Notes 9 and 10, *Caution:* flames). Continue the agitation until addition compounds with aluminum chloride are decomposed *completely*. Separate the benzene phase in a separatory funnel, and extract the aqueous phase once with more benzene. Remove aluminum chloride by several washings with water, and remove acid with aqueous base. Wash finally with water. Dry with a suitable drying agent, and strip off the benzene, bearing in mind the small volume and high boiling point of the product (Note 11). Collect the product over a 5° range near the boiling point, and determine the percentage yield (Note 12).

Notes

1. The agitation can be carried out manually, but in that case the yield usually is lower.
2. Hydrogen chloride must not be allowed to escape into the atmosphere. Since the amount evolved when acetic anhydride is used is comparatively small, a simple system is sufficient, in this case.
3. Thiophene-free benzene is best but is not essential.
4. It is essential that the benzene be dry. It should be shaken for some time with anhydrous calcium chloride. Filtering through a plug of cotton removes the solid sufficiently well.
5. Unless the aluminum chloride is anhydrous, the experiment will be a failure. Refer to 29.13, for testing. The powdered form is preferred over the lump form, but either is satisfactory.
6. There is no danger of the reaction getting out of hand, even in the case of acetyl chloride, which is more reactive than the anhydride. However, the yield is lower if the addition is made rapidly.
7. In case acetic anhydride is used, refer to 36.16, for the amount of catalyst to take. Heat much longer, since the reaction is slower.
8. Note that two phases are present.
9. In case acetyl chloride was taken, the amount of hydrochloric acid can be decreased.

10. Refer to 6.16 in case an emulsion results. The addition of ether is sometimes helpful. Steam distillation may be necessary.

11. Refer to Subsection 9.15.

12. Yield is 75% with acetyl chloride and somewhat less with the anhydride.

Questions

1. What types of halogen compounds may be used in the Friedel–Crafts synthesis?

2. What modifications may be made if an aromatic hydrocarbon is to be prepared, instead of a ketone?

3. How can you account for the fact that the yield usually is low when shaking is by hand?

4. Which reagent is in excess in this experiment, and why?

5. What are the two liquid phases in the reaction mixture?

6. Why not decompose the product with water, instead of with dilute hydrochloric acid?

7. Is hydrogen chloride soluble in benzene?

8. Why is the benzene washed with water first?

9. State three modifications of the Friedel–Crafts synthesis of benzophenone.

10. What is the maximum yield possible with 0.2 mole of acetic anhydride?

11. What are the probable impurities in the product, and what steps have been taken to remove them?

Experiment 36–2   Preparation of 2-(4'-Bromobenzoyl)benzoic Acid

To a 500-ml. flask fitted with an air condenser and an arrangement for absorbing evolved hydrogen chloride (Note 1), add 0.05 mole of finely ground phthalic anhydride, 0.15 mole of bromobenzene (Note 2), and 0.2 mole of *anhydrous* aluminum chloride (Note 3). By means of a steam bath or oil bath heat slowly to 95° (Note 4) over a period of an hour, and keep at 95° for 2 hours. Stir *frequently*, but avoid spreading the mixture over the walls of the flask (Note 5). Disconnect the flask from the apparatus, and add *rapidly* about 100 ml. of water followed by about 100 ml. of 6 N hydrochloric acid (Note 6). Steam-distil until all the bromobenzene has been removed. Remove the hot liquid by decantation from the residue, and wash a few times with hot 2 or 3 N hydrochloric acid. Spread the gum while still warm, over the inside surface of the flask, to facilitate the dissolving process.

Dissolve the residue by first adding 30 ml. of concentrated ammonium hydroxide, followed by the gradual addition of water up to 0.4 to 0.5 liter. Heat quickly to boiling, maintain near boiling with gentle agitation until the desired acid is dissolved (Note 7), add some filter aid (Note 8), and filter so as to obtain a hot clear filtrate. Cool the filtrate (Notes 9 and 10), and throw out the desired acid by adding hydrochloric acid. As the point of precipitation is approached, add the acid

drop by drop and with stirring, from then on. Add sufficient to neutral-
ize all the original ammonium hydroxide. Collect the product by suction
filtration, and, after thorough drying, take the melting point (Note 11).
Crystallize the product from toluene if not pure (refer to 5.22, etc.).

Notes

1. Hydrogen chloride is evolved when anhydrous aluminum chloride is heated
with many aromatic compounds. A sealed mechanical stirrer is advantageous, but
yields are almost as good without it.

2. An excess of bromobenzene is desirable, to act as solvent.

3. It is essential that the aluminum chloride be anhydrous. Refer to discussion,
Chapter 29, for testing. If the aluminum chloride does not sublime completely and
the residue is not too great, allow for presence of inert material.

4. At higher temperatures dibromodiphenylphthalide is formed. If a steam bath
is used, take care that water does not get into the flask.

5. The mixture may stand overnight at this step or at other subsequent steps.

6. The hydrochloric acid prevents precipitation of aluminum hydroxide. On ac-
count of the high heat of hydration of anhydrous aluminum chloride, the addition
should be rapid. Otherwise there is excessive local heating.

7. Since continued boiling will drive out ammonia, add more.

8. If this is diatomaceous earth, 5 g. should suffice for obtaining a clear filtrate.

9. The solid that separates at this point is the ammonium salt. This can be
converted into reasonably pure acid. To the clear filtrate (before any salt has sep-
arated) add a clear aqueous solution of an ammonium salt containing about 0.5
mole of ammonium ion. Cool and let stand, or stir, until crystallization is complete.
Collect the solid by suction filtration and wash it with a cold ammonium salt solu-
tion. Decompose it by the gradual addition of hydrochloric acid (about 1 N) to a
suspension of the solid in water, as given in the directions. Yield of acid, m.p.
158–162°, 60%. Acid of this melting point is sufficiently pure for Experiment 38–3.
The purity is lower if the solution is cloudy.

Acidification of the filtrate yields some impure acid which can be purified by con-
version to the ammonium salt, as previously, or by crystallization.

10. If the solution is not cold, the acid usually separates as an oil and then is less
pure.

11. The product sublimes near the melting point, which is 173°. Either heat the
bath to near the final temperature before putting in the sample, or seal off the melting-
point tube. Yield is 70%.

Questions

1. Write the structure of 2-(4'-bromobenzoyl)benzoic acid.

2. What is formed when this compound is heated with concentrated sulfuric acid?

3. What impurities do you think the crude product, after precipitation by ad-
dition of hydrochloric acid, may contain?

4. What is formed when ammonium hydroxide is added?

5. What impurities are removed by dissolving in ammonium hydroxide, filtering,
and precipitating by the addition of hydrochloric acid?

6. What simpler ketone can be prepared by the Friedel–Crafts synthesis using an
anhydride? Write the equation.

7. How may benzophenone be prepared by different modifications of the Friedel–Crafts synthesis?

8. Why is the molal ratio of aluminum chloride to anhydride so large?

9. What side reactions take place?

Experiment 36–3   Properties of Aldehydes and Ketones

IDENTIFICATION, BY FORMATION OF 2,4-DINITROPHENYLHYDRAZONE. In a 15-ml. centrifuge tube place about 0.1 g. (0.0005 mole) of 2,4-dinitrophenylhydrazine (Note 1) and 1 ml. of glacial acetic acid (Note 2). Heat to gentle boiling until the solid has dissolved, and while still hot add 3 to 5 drops of acetophenone or about 0.1 g. of benzophenone. Keep hot for 1 to 2 minutes. The 2,4-dinitrophenylhydrazone separates on cooling (Note 3).

Centrifuge, and wash two or three times with acetic acid or alcohol, centrifuging down each time. Crystallize from hot alcohol (Note 4), and take the melting point (Note 5).

Obtain an unknown aldehyde or ketone from the instructor, and identify it by conversion to the 2,4-dinitrophenylhydrazone.

Notes

1. The amount designated is sufficient for a derivative. Do not take more, because it is an expensive chemical.

2. Although the reaction often takes place rapidly in acetic acid alone, addition of a very small amount of sulfuric acid sometimes is desirable, because it catalyzes those reactions that otherwise would be slow, as for example the one with benzophenone.

3. Some 2,4-dinitrophenylhydrazones separate soon after the carbonyl compound is added, others on cooling, and still others only after water has been added (drop by drop). If the last is the case, a blank must be run also, in order that the amount of water which causes the reagent itself to separate may be known.

4. Acetic acid, ethyl acetate, or chloroform is a satisfactory solvent. In case the solid is insoluble in these, crystallize from hot nitrobenzene. Naturally, this solvent, being high boiling, must be removed by washing with a volatile solvent.

5. 2,4-Dinitrophenylhydrazine melts at 198° with decomposition. The melting points of many 2,4-dinitrophenylhydrazones can be found in *Qualitative Organic Analysis* by Kamm, or in *Identification of Organic Compounds* by Shriner and Fuson (refer to Section 46.1, Note 1).

Questions

1. Write the equation for the reaction of 2,4-dinitrophenylhydrazine with acetophenone.

2. Name three other reagents that are useful in the identification of aldehydes and ketones.

3. What are the relative advantages and disadvantages of these reagents?

4. Compare them with 2,4-dinitrophenylhydrazine in these respects.

AROMATIC CARBOXYLIC ACIDS

The methods by which aliphatic carboxylic acids can be prepared are applicable in general to the aromatic acids. Other methods of preparing aromatic acids are: (a) nitrile synthesis from sulfonic acids or from diazonium compounds followed by hydrolysis of the resulting nitrile, (b) oxidation of side chains, (c) the condensation of acid anhydrides with benzaldehyde or substituted benzaldehydes (the Perkin condensation), (d) the carboxylation of phenols (the Kolbe condensation), (e) the Friedel–Crafts condensation with phosgene:

(a) $C_6H_5SO_3K + KCN \longrightarrow C_6H_5CN + K_2SO_3$

$C_6H_5N_2Cl + NaCN \xrightarrow{CuCN} C_6H_5CN + N_2 + NaCl$

$C_6H_5CN + 2H_2O + H_2SO_4 \longrightarrow C_6H_5COOH + NH_4HSO_4$

(b) $C_6H_5C_2H_5 + 4KMnO_4 \longrightarrow$

$C_6H_5COOK + 4MnO_2 + KOH + K_2CO_3 + 2H_2O$

$2C_6H_5COOK + H_2SO_4 \longrightarrow 2C_6H_5COOH + K_2SO_4$

(c) $C_6H_5CHO + (CH_3CO)_2O + NaOOCCH_3 \xrightarrow{180°}$

$C_6H_5CH{=}CHCOONa + 2CH_3COOH$

(d) $C_6H_5ONa + CO_2 \longrightarrow C_6H_5OCOONa$

$C_6H_5OCOONa \xrightarrow{heat}$

 $+ HCl \longrightarrow$ $+ NaCl$

(e) $C_6H_6 + COCl_2 + AlCl_3 \longrightarrow C_6H_5COCl \cdot AlCl_3 + HCl$

$C_6H_5COCl \cdot AlCl_3 + H_2O \xrightarrow{HCl} C_6H_5COOH + HCl + AlCl_3$

37.11 Hydrolysis of Nitriles. In method a the hydrolysis reaction is catalyzed by acids or bases and usually is carried out in hot aqueous solutions. Sometimes alcohol is added in order to increase the solubility

of the nitrile. Sulfuric acid containing only a small amount of water, as for example 80% sulfuric acid, often will cause rapid hydrolysis of nitriles to acids, because the nitrile is more soluble than at lower concentrations of acid and the temperature can be carried higher. However, in some cases, for example phenylacetic acid, the yield of acid is poor with 80% sulfuric acid, probably because sulfonation takes place. A weaker acid, about 55% is preferable, as in Experiment 37–2.

The hydrolysis of nitriles in aqueous solution is more strongly exothermic than 9 kcal., which is the calculated value for the gas-phase reaction, mainly because of the heat of neutralization of ammonia with sulfuric acid or of the organic acid with the strong base, depending on which catalyst is used.

The nitrile group can be attached to the benzene nucleus by replacement of a sulfonic acid group or a diazonium group. When an intimate mixture of potassium or sodium benzene sulfonate and potassium cyanide is heated, phenyl cyanide distils out as formed. The Sandmeyer and Gattermann methods of nitrile preparation from diazonium salts are discussed in 34.24.

The nitrile group can be attached to a side chain by the methods discussed in Chapter 28. Benzyl cyanide (Experiment 37–1) is prepared from benzyl chloride by a reaction with sodium cyanide.

37.12 Oxidation of Side Chains. In method *b* oxidation may be accomplished by dichromate (or chromic anhydride) in hot aqueous sulfuric acid, or in warm moderately concentrated sulfuric acid; by hot dilute nitric acid; or by permanganate in a hot alkaline aqueous solution. In general, side chains are oxidized away, leaving one carbon atom attached to the ring as part of the carboxyl group. Dialkylated benzenes may be oxidized to monobasic as well as to dibasic acids. Thus, *p*-xylene may be converted either to *p*-toluic acid or to terephthalic acid. Amino and hydroxy groups if present must be "protected" by acylation before oxidation is attempted; otherwise, the ring is opened, and an aliphatic compound is formed. Often dichromate oxidation also causes destruction of the benzene ring when an *ortho* substituent is present, as for example, *o*-bromotoluene. However, 2,4,6-trinitrotoluene is oxidized to 2,4,6-trinitrobenzoic acid by dichromate and warm concentrated sulfuric acid. Under these conditions the reaction is markedly exothermic.

Aqueous oxidizing agents usually have two disadvantages: (1) the organic material is only slightly soluble, and (2) it usually is necessary to apply heat, which may cause the compound to steam-distil unless a reflux condenser is used. Nitric acid has the added disadvantage that, even if dilute, it may cause some nitration. Also potassium perman-

ganate is so slightly soluble in water that large volumes are necessary. For this reason potassium permanganate sometimes is replaced by a more soluble permanganate, such as calcium permanganate. Sometimes a solution of potassium permanganate in acetone is used.

37.13 The Perkin Synthesis. Method c is valuable for the synthesis of unsaturated acids with the carboxyl group on a side chain. It is carried out by heating the reactants for several hours at 180°.

37.14 Carboxylation of Phenols. In method d phenols can be converted directly to hydroxy acids by carbon dioxide. Sodium phenoxide is converted into sodium salicylate at 130° to 140° in the Kolbe synthesis, whereas potassium phenoxide at 180° is converted into potassium p-hydroxybenzoate. A second hydroxyl group *meta* to the first increases the reactivity, as shown by the fact that resorcinol and pyrogallol are carboxylated at 100° in aqueous potassium bicarbonate. It is possible to carboxylate benzene, but only at high temperatures and pressures.

37.15 The Friedel–Crafts Synthesis. In method e a modification leads to the synthesis of an acid chloride by the use of phosgene. The acid chloride may be hydrolyzed to the acid. However, this synthesis is complicated by a subsequent reaction, the formation of a ketone (refer to 36.16).

Experiment 37–1 Preparation of Benzyl Cyanide

In a 500-ml. flask place 1 mole of granular or powdered sodium cyanide (*Caution:* Notes 1 and 2), 40 to 50 ml. of pure water (Note 3), 0.80 mole of benzyl chloride (b.p. 173–179°) (Notes 4 and 5), and 100 ml. of alcohol. Attach a reflux condenser (previously fitted), and heat on an oil bath so that the mixture boils fairly vigorously. Reflux (Note 6) as long as the desired reaction seems to be taking place (Note 7), remove the reflux condenser, distil over the alcohol by heating in an oil bath (Note 8), and stop when the distillate is largely water, for then benzyl cyanide steam-distils.

Cool, and add enough pure water to dissolve the salt and residual alcohol. Separate in a separatory funnel. In case a troublesome emulsion is encountered, return the liquid to the reaction flask, add a suitable filter aid, shake well (Note 9), and filter with suction. Draw water two or three times through the filter cake to remove entrained oil. Separate in a separatory funnel (Note 10), and shake a few times with water to remove alcohol and sodium cyanide. Dispose of filter cake and washings in the hood sink with a good stream of water. Wash twice with cold, moderately concentrated (25 to 30%) sulfuric acid to remove isocyanide,

then with water a few times, and finally with aqueous carbonate to remove sulfuric acid.

Without needless delay distil at 30 mm. (Notes 11 and 12) from a Claisen type flask with a short fractionating column in the neck. In case ether had been added, remove this carefully at ordinary temperature by reducing the pressure slowly. Then heat the bath fairly rapidly to 90–110°. Remove water rapidly until the distillation temperature is *ca.* 50° at 30 mm. Then dry out the condenser, change the receiver, and continue the distillation, collecting the benzyl cyanide over a 5° range. Calculate the percentage yield (Notes 13 and 14).

Notes

1. *Caution:* Sodium cyanide is a **deadly** poison. It is absorbed quickly through breaks in the skin, for example a cut, and may cause death. Do not allow it to remain on the skin, but wash it off at once. Also, clean up immediately and thoroughly any that may be spilled.

2. The commercial Cyanegg (sodium cyanide in 1-oz. egg-shaped pieces, 96 to 98% pure) is best, because it does not deteriorate so rapidly as granules or powder. The large lumps should be broken up into smaller pieces in a *large* mortar, care being taken that small pieces are not scattered on the floor or the chemical desk.

3. Emulsion formation later is liable to be more troublesome if calcium ions are present, owing to insoluble calcium sulfate.

4. From Experiment 30–3; the yield from benzyl chloride of this boiling range should be about 80%. The yield is lower if the chloride is less pure.

5. *Caution:* Benzyl chloride is a lachrymator. Make all transfers in the hood. In case any is spilled, wash up with alcoholic base.

6. The composition of the solvent will change if the condensing is not effective. It is not necessary that all of the sodium cyanide be dissolved initially.

7. A solid crystallizes as the reaction takes place. Heating for 4 hours gives a yield of about 80%, and for 7 hours about 90%.

8. The benzyl cyanide is somewhat soluble in an alcohol–water mixture.

9. Removal of the insoluble colloidal polymer at this point usually is desirable; otherwise, a rather stable emulsion may result. The polymer usually can be removed by adding diatomaceous earth and filtering.

10. If the phases do not separate well, refer to Subsection 6.16, Emulsions. Ethyl ether is preferred in case a diluent is desirable.

11. The liquid often darkens on standing, owing to polymerization.

12. See Chapter 8. Before starting the distillation, obtain the approval of the instructor in regard to the setup and to the air inlet tube.

13. Boiling point: 127–128° at 30 mm., 107–108° at 12 mm. Use Figure 8–2 to obtain boiling points at other pressures. If the distillation is carried out at atmospheric pressure (b.p. 233–234°, cor.) at 760 mm., a white solid usually separates during the distillation.

14. The residue in the distilling flask dissolves readily in acetone. Pour the washings down the hood sink, because of the disagreeable odor.

Questions

1. Why is the solvent in this experiment a mixture of water and alcohol?
2. Why is it not necessary that all the sodium cyanide be completely dissolved initially?
3. Is there any advantage in not having the sodium cyanide completely in solution initially?
4. What disadvantage may be connected with incomplete condensing during the refluxing?
5. Why should the boiling be fairly vigorous?
6. What solid crystallizes out as the heating is continued?
7. Why is heating done by a liquid bath while the alcohol is being removed by distillation?
8. Why bother to remove the alcohol anyway?
9. What conditions favor the formation of stable emulsions?
10. Which one of these operates in this case?
11. Explain why filtering is desirable.
12. What is the function of the diatomaceous earth?
13. Why is 25–30% sulfuric acid effective in removing any isocyanide?
14. How does this compound differ in structure from benzyl cyanide?
15. Why not use concentrated sulfuric instead?
16. Write equations for the most convenient methods of preparing: (a) methyl cyanide, (b) n-butyl cyanide, (c) phenyl cyanide.
17. What are the probable impurities in the crude and final products?
18. What steps are taken to remove them?

Experiment 37–2   Preparation of Phenylacetic Acid

Set a 500-ml. flask with reflux condenser attached on a single support so that it can be shaken as a unit. Add and heat to a temperature of gentle refluxing 0.40 mole of benzyl cyanide with 250 to 300 g. of 55% (by weight) sulfuric acid (Notes 1 and 2), shaking at frequent intervals until it is converted completely to the desired acid (Note 3).

Allow the reaction mixture to cool somewhat (to 80° or 90°), and pour it (*Hood*) slowly during vigorous stirring into a volume of water sufficient to reduce the concentration of the sulfuric acid to 25 or 30% (Notes 4 and 5). Allow the mixture to stand until cold. The dark upper layer should solidify, and the aqueous phase should be colorless and should be filled with a mass of crystals. Cool to 0°, and keep at this temperature for 0.5 to 1 hour, stirring frequently. Collect the solid by suction filtration (Notes 6 and 7).

Dissolve the crude phenylacetic acid in dilute aqueous ammonia (1 *N*), adding this a little at a time towards the last until the liquid is just alkaline (Notes 8 and 9). Let stand for 10 to 15 minutes with decolorizing carbon and filter aid (see Chapter 5), stirring at intervals. Filter

through a large fluted filter, previously wet with water. Cool to below room temperature. Precipitate the organic acid by the slow addition of cold sulfuric acid, 3 to 6 N (Note 10).

In case a white oil emulsion separates at first and will not solidify on cooling and stirring, remove it by filtering through the same filter, and repeat if necessary (Note 11). Finally, after crystals form, slowly add sufficient acid to cause complete precipitation. Cool, let stand cold for an hour or more, stir frequently, filter with suction, wash with small portions of cold water until sulfate-free, dry, take the melting point, and calculate the percentage yield (Note 12).

Notes

1. To obtain the correct concentration, the strength of sulfuric acid available should be known.

2. At the refluxing temperature of the mixture, 135–140°, the reaction takes place with reasonable rapidity, usually in 1 to 2 hours. With 60% acid the time is somewhat shorter, but the reaction mixture is darker. With 70% acid the reaction is quite vigorous for ½ to 1 minute. However, the reaction mixture then is quite dark, and much difficulty is encountered in obtaining a crystalline product since some of the nitrile probably does not react. If the mixture is heated longer, darkening increases, and, when the reaction mixture is poured into water, little or no solid separates, probably because sulfonation has taken place.

Refluxing with concentrated hydrochloric acid for 2 or 3 days gives a good yield of easily purified acid.

3. Test by removing a drop of the upper phase at intervals of about ¼ hour. A drop becomes solid on cooling after much of the nitrile has been converted. To get most of the nitrile converted, heat about as long again. It is desirable to hydrolyze the nitrile completely; otherwise, oil formation is troublesome later during purification of the product.

4. Dilution with water is desirable because: (1) Sulfuric acid more concentrated than about 30% does not filter well through filter paper; (2) the phenylacetic acid separates in a form more satisfactory for filtering when the concentration of sulfuric acid is reduced to 25 or 30%; (3) the solubility of phenylacetic acid is greater, the higher the concentration of sulfuric acid. The solubility of phenylacetic acid in water at 20° is 1.7 g. per 100 g. and in 20 or 25% sulfuric acid is higher.

5. Do as much of the work as possible in the hood from this point on. Avoid spilling any of the solution or solid, because of its persistent disagreeable odor, which may remain in the clothes for days. Rubber gloves may be worn, if desired.

6. Phenylacetic acid has a pronounced tendency to form supersaturated solutions. It is well to save the filtrate to see if more solid separates. The filtrate could be used later for precipitating phenylacetic acid from the solution of the ammonium salt.

7. Or the solidified upper layer may be removed and dissolved in ammonia, as described, and the aqueous acid phase, if colorless, may be added to the resulting ammoniacal solution with the proper precautions. Less product then is lost in the filtrate.

8. If too large an excess of ammonia is added, impurities may be dissolved. These tend to come out of solution at the beginning of the acidification process with the re-

sult that some of the phenylacetic acid separates as an oil. It is well to know the amount of ammonia required, since this determines the minimum amount of acid to be added later.

9. If the ammonia is too concentrated, addition of water to a part of the liquid sometimes causes an oil to separate. In case a more concentrated solution is added, dilute finally to about 400 ml. before filtering. ·

10. Hydrochloric acid can be used in place of sulfuric acid, but the latter is better, since ammonium sulfate is much more soluble than ammonium chloride, and in presence of excess acid the solubility increases rather than decreases.

11. Since the oil is composed largely of phenylacetic acid, much product can be lost at this point. Small test portions of 0.5 to 1 ml. can be acidified at different temperatures, to get the best conditions. These vary with different experiments, owing to differences in purity of benzyl cyanide, and in extent of hydrolysis.

12. Yield is 70%.

Questions

1. Explain why the rate of hydrolysis of benzyl cyanide at the refluxing temperature in the presence of an inorganic acid is in the order:

$$70\% \text{ H}_2\text{SO}_4 > 60\% \text{ H}_2\text{SO}_4 > 50\% \text{ H}_2\text{SO}_4 > \text{concd. HCl}$$
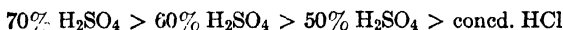
2. Is the hydrolysis a one-step reaction? Explain.

3. Why is it desirable to wet the filter paper with water before filtering the solution of the ammonium salt?

4. Why is it better to filter this solution through a fluted filter paper, rather than to use suction?

5. Does water have any effect on the tendency of phenylacetic acid to change from a solid to a liquid?

6. Explain why an excess of sulfuric acid has one effect on the solubility of ammonium sulfate whereas an excess of hydrochloric acid has a different effect on the solubility of ammonium chloride.

7. What are the equations for the reactions involving benzyl cyanide and phenylacetic acid, in the experiment as carried out?

8. What other type of reagent could be used for the conversion of benzyl cyanide to phenylacetic acid?

9. What are the probable impurities in the crude and final products?

10. What steps have been taken to remove them?

Experiment 37–3   Preparation of Potassium
o-Sulfo-p-nitrobenzoate

In a 2- or 3-liter flask dissolve 0.1 mole of potassium p-nitrotoluene-o-sulfonate in 1 liter of hot water. Add a solution of 0.15 mole of potassium hydroxide (Note 1) in 0.2 liter of hot water, and heat by a hot water or a steam bath. Add a 50% excess of solid potassium permanganate, and stir until it is completely dissolved. Keep the mixture hot until the permanganate color disappears (Note 2), testing from time to time for the presence of permanganate (Note 3). Add 5 to 10 g. of filter aid, and collect the precipitated manganese dioxide by suction filtration

while the liquid is hot (Note 4). To wash the filter cake, remove it to a beaker, add enough hot water to make a thin mush, stir well, and again filter.

Bring the combined filtrates to neutrality with c.p. hydrochloric acid (Note 5), and evaporate in a large evaporating dish until a drop of the solution, when held on the end of a stirring rod, becomes largely crystalline on cooling. Allow the solution to cool. Collect the dipotassium salt of o-sulfo-p-nitrobenzoic acid by suction filtration. Draw off as much of the liquid as possible. Wash the solid as above in a beaker of suitable size with some water, and filter again by suction, having first transferred the previous filtrate to another vessel. Use the second filtrate to wash out the beaker in case some of the solid remains behind.

Combine the two filtrates, and while stirring or shaking add sufficient c.p. concentrated hydrochloric acid to furnish 0.1 to 0.2 mole of hydrogen chloride (Note 5). The acid potassium salt of o-sulfo-p-nitrobenzoic acid separates. Collect and wash this in the same way. Dry the two salts separately, and determine the percentage yield (Note 6).

Notes

1. Commercial grade is satisfactory. Any iron present is removed when the solution is filtered.
2. This usually requires 2 to 4 hours.
3. A simple test for permanganate in the dark-colored mixture consists in dropping a small portion onto filter paper. The insoluble manganese compound remains stationary whereas the solution spreads.
4. The suction flask should first be heated by placing warm water in it. Otherwise, it may break when the hot liquid strikes it. The filtration may be done with a large fluted coarse filter, instead of using suction, but this is less satisfactory.
5. Commercial hydrochloric acid contains iron, which is carried down to some extent by the product.
6. The combined yield is 85% of theoretical.

Questions

1. Why is an excess of permanganate taken?
2. Which is more soluble in cold water, the mono- or the dipotassium salt?
3. What is the formula of the monopotassium salt?
4. What reagents are used for side-chain oxidations?
5. Why is permanganate preferred over dichromate in this oxidation?
6. Why is suction filtration from the manganese dioxide preferable to gravity filtration?
7. Explain why the amount of hydrochloric acid added in the last step is greater than theoretically required by the equation.
8. Which product is more likely to be contaminated by any unoxidized potassium p-nitrotoluene-o-sulfonate?

Chapter 38

QUINONES

Quinones may be obtained by: (*a*) the rapid and reversible oxidation of the corresponding dihydric phenol, (*b*) the oxidation of aminophenols, diamines, phenols, and amines, (*c*) oxidation of hydrocarbons. Anthraquinone and derivatives usually are prepared by another method: (*d*) ring closure of *o*-benzoylbenzoic acid and derivatives.

(*a*) $\quad 3p\text{-}C_6H_4(OH)_2 + KBrO_3 \rightarrow 3O{=}C_6H_4{=}O + KBr + 3H_2O$

(*b*) $\quad p\text{-}NH_2C_6H_4OH + 2FeCl_3 + H_2O \rightarrow$

$$O{=}C_6H_4{=}O + 2FeCl_2 + HCl + NH_4Cl$$

$$3p\text{-}C_6H_4(NH_2)_2 + KBrO_3 + 3H_2O + 6HCl \rightarrow$$

$$3O{=}C_6H_4{=}O + KBr + 6NH_4Cl$$

$$6C_6H_5NH_2 + 4K_2Cr_2O_7 + 19H_2SO_4 \rightarrow$$

$$6O{=}C_6H_4{=}O + 4Cr_2(SO_4)_3 + 3(NH_4)_2SO_4 + 4K_2SO_4 + 16H_2O$$

(*c*)

$$+ 2CrO_3 + 6CH_3COOH \rightarrow$$

$$+ 2Cr(OCOCH_3)_3 + 4H_2O$$

(*d*)

$$\rightarrow$$

$$+ H_2O$$
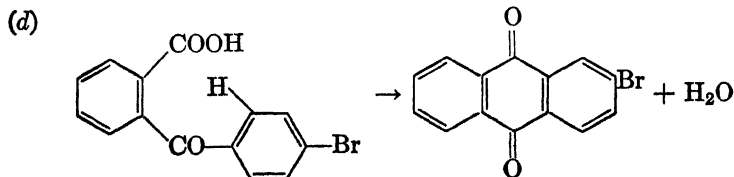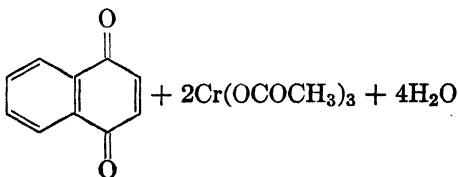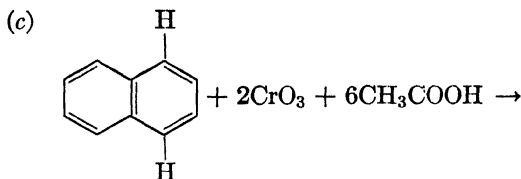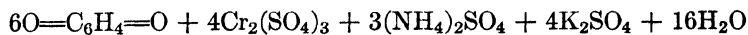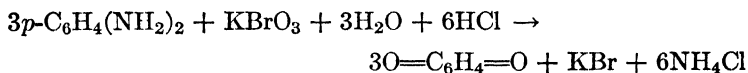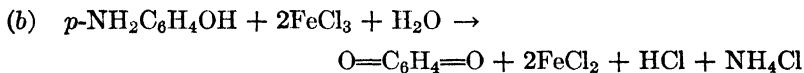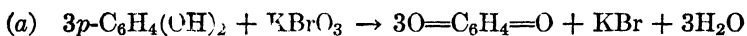
38.11   Reversible Oxidation of Dihydric Phenols (1,2- and 1,4-). In method a dihydric phenols are oxidized easily to the corresponding quinones. The quinhydrone separates at first as the reaction proceeds, but, after the half-point of oxidation is reached, it slowly disappears, and the quinone itself may separate if the volume of the solution is not too large.

The oxidation of dihydric phenols to quinones is reversible and very rapid. The molal reduction potentials $E°$ of various dihydric phenols going to their quinones according to the equation,

$$\text{Dihydric phenol} \rightleftharpoons \text{quinone} + 2H^+ + 2e^-$$
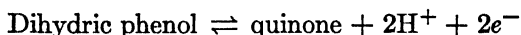
can be determined (see Subsection 1.44). In Table 38–1 are listed values of $E°$ at 25° for various dihydric phenols going to their corresponding quinones. In Subsection 1.44 the method of calculating an equilibrium constant K in an oxidation–reduction reaction is discussed.

The equilibrium constant K for the reaction between ferric ion as oxidizing agent and hydroquinone as reducing agent is given by equation 1–43 which is repeated here:

$$K = 21 = \frac{(p\text{-benzoquinone})(H^+)^2(Fe^{++})^2}{(\text{hydroquinone})(Fe^{+++})^2}$$

Thus when the concentrations of H^+, Fe^{++}, and Fe^{+++} are 1 molal, the ratio quinone to hydroquinone is 21. The value of this ratio can be increased and thus the reaction shifted further towards completion from the standpoint of the organic components, by increasing the concentration of Fe^{+++} or by decreasing the concentration of Fe^{++} or H^+.

The most important concentration is that of the hydrogen ion, since it is the easiest to vary or to maintain at a constant value through buffering. Thus, when the solution is buffered by sodium acetate at pH 6, the ratio quinone to hydroquinone is 2×10^9 when only 1% excess ferric ion is taken. If exactly two equivalents of ferric ion are taken, less than 0.1% of the hydroquinone remains unoxidized at equilibrium. Under these conditions the oxidizing action of ferric ion drives the reaction essentially to completion. The important role of the hydrogen-ion concentration in many cases permits oxidizing agents of much lower potential to be used in the oxidation of hydroquinone. Thus ferricyanide ion of potential -0.49 can efficiently oxidize hydroquinone of potential -0.70.

The values of the molal reduction potential of dihydric phenols show that pyrocatechol 1,2-$C_6H_4(OH)_2$ requires a more powerful oxidizing agent than hydroquinone, since its reduction potential is lower, namely,

—0.79 volts whereas 9,10-anthracenediol has a higher reduction potential, namely, —0.15 volt, which makes it more susceptible to oxidation (see Table 38–1).

When bromate is the oxidizing agent, as in the preparation of quinone from hydroquinone (Experiment 38–1), the reaction is promoted by hydrogen ion. The acidity must not be too great; otherwise, the reaction may proceed so rapidly that control is difficult and at the same time bromine is liberated. This causes the product to be dark colored. For this reason also there should be only a slight excess of bromate, and the acidity should be low also, since the rate of formation of bromine is second order with respect to hydrogen-ion concentration.

38.12 Oxidation of Aminophenols, Diamines, Phenols, and Amines. In method b, aminophenols (1,2- and 1,4-) are reversibly and easily oxidized to quinone monoimines; and diamines (1,2- and 1,4-) to quinone diimines. Imines rapidly hydrolyze to quinones in dilute aqueous acid. Aminonaphthols are especially useful in preparing naphthoquinones, since they are obtained easily by the reduction of nitronaphthols.

The oxidation of phenols and amines to quinones takes place comparatively slowly and is nonreversible. *para*-Quinones are formed when possible. The oxidizing agent must be one that does not attack quinones. The latter generally are stable to dichromic acid at room temperature. Yields are best from monohydric phenols and monobasic amines if the oxidation is carried out without much heating.

<div align="center">

TABLE 38-1

MOLAL REDUCTION POTENTIALS OF VARIOUS DIHYDRIC PHENOLS AT 25°C.

</div>

			$E°_{298}$ Volts	
			Aqueous	Alcoholic
Hydroquinone	⇌ 1,4-Benzoquinone	$+ 2H^+ + 2e^-$	—0.699	—0.715
Pyrocatechol	⇌ 1,2-Benzoquinone	$+ 2H^+ + 2e^-$	—0.794	
Methylhydroquinone	⇌ Methyl-1,4-benzoquinone	$+ 2H^+ + 2e^-$	—0.645	—0.656
Hydroxyhydroquinone	⇌ Hydroxy-1,4-benzoquinone	$+ 2H^+ + 2e^-$	—0.594	—0.599
Chlorohydroquinone	⇌ Chloro-1,4-benzoquinone	$+ 2H^+ + 2e^-$	—0.713	—0.736
Tetrachlorohydroquinone	⇌ Tetrachloro-1,4-benzoquinone	$+ 2H^+ + 2e^-$		—0.703
1,4-Naphthalenediol	⇌ 1,4-Naphthoquinone	$+ 2H^+ + 2e^-$	—0.470	—0.484
1,2-Naphthalenediol	⇌ 1,2-Naphthoquinone	$+ 2H^+ + 2e^-$	—0.555	—0.576
2,6-Naphthalenediol	⇌ 2,6-Naphthoquinone	$+ 2H^+ + 2e^-$		—0.76
1,4-Anthracenediol	⇌ 1,4-Anthraquinone	$+ 2H^+ + 2e^-$		—0.401
1,2-Anthracenediol	⇌ 1,2-Anthraquinone	$+ 2H^+ + 2e^-$		—0.490
9,10-Anthracenediol	⇌ 9,10-Anthraquinone	$+ 2H^+ + 2e^-$		—0.154
1,4-Phenanthrenediol	⇌ 1,4-Phenanthrenequinone	$+ 2H^+ + 2e^-$		—0.523
1,2-Phenanthrenediol	⇌ 1,2-Phenanthrenequinone	$+ 2H^+ + 2e^-$		—0.660
3,4-Phenanthrenediol	⇌ 3,4-Phenanthrenequinone	$+ 2H^+ + 2e^-$		—0.621
9,10-Phenanthrenediol	⇌ 9,10-Phenanthrenequinone	$+ 2H^+ + 2e^-$		—0.460

38.13   Oxidation of Hydrocarbons. In method c oxidation usually is carried out with chromic anhydride in glacial acetic acid, which dissolves both reactants. The method is satisfactory with fused-ring hydrocarbons such as naphthalene, anthracene, and phenanthrene, as in Experiment 38–2, the Preparation of Naphthoquinone.

38.14   Anthraquinone Condensation. Method d is important industrially, since many useful dyes are derived from anthraquinone (alizarin and other mordant dyes; indanthrene and other vat dyes). Two essential conditions for this reaction are: (1) a sufficiently high temperature and (2) a strongly acid medium. The reaction proceeds well in hot concentrated sulfuric acid (150°). Sometimes fuming sulfuric acid is best. The rate of the reaction at 75° in 100% sulfuric acid is twice that in 95% acid, and this is greater than in more dilute acid.

From kinetic studies it is known that the reaction to form the anthraquinone is first order with respect to the benzoylbenzoic acid. As the concentration of the latter increases, the second-order reaction to form a linear dimer becomes more important. The concentration therefore should be kept low to minimize the latter reaction.

38.15   Purification of Quinones. This should be done at as low a temperature as possible, because of the tendency of quinones to darken when heated. In general the least stable quinones are those whose corresponding diols have the lowest reduction potential, Table 38–1. Even 9,10-anthraquinone, the most stable of the quinones listed, decomposes slowly at its boiling point.

Experiment 38–1   Preparation of p-Benzoquinone

In a 200-ml. conical flask place 0.10 mole of hydroquinone, a 5% excess of potassium bromate (refer to 38.11), and 100 ml. of water (Note 1). Heat the mixture to 60° (Note 2), and agitate to dissolve all solid. The solution darkens somewhat, owing to the formation of some quinhydrone. Add 5 ml. of 1 N sulfuric acid (Note 3), and mix thoroughly. The reaction starts promptly, the mixture becomes dark colored, and the temperature slowly rises spontaneously to 75° (Note 4). As soon as any quinhydrone separates, agitate more or less continuously. In 10 to 15 minutes the solution and solid become a clear yellow. If the temperature exceeds 80°, cool slightly. Heat the mixture *quickly* to 80°, agitate until the solid has largely dissolved (Notes 5 and 6), and cool rapidly to about 50°. Cool slowly, finally to 0°, and let stand at this temperature for about 0.5 hour with frequent agitation.

Collect by suction filtration, and wash twice with about 10-ml. portions of ice water. Dry *rapidly* and *completely*, weigh, and determine

the melting point (Notes 7 and 8).   The product may be purified further by sublimation (see Chapter 11).

Notes

1. With this amount of water, the quinone will be completely or almost completely dissolved at 80°.

2. In case the experiment is carried out with larger quantities, the initial temperature should not be above 50°; otherwise, the final temperature may be too high.

3. The concentration of acid is critical.   If the acid concentration is low by as much as 15%, heat must be applied in order to maintain a satisfactory temperature, since spontaneous heating does not take place.   The product is dark colored.   If the final acid concentration is as high as 0.1 N, the oxidation proceeds quite rapidly and is complete in 1 or 2 minutes, but the result is not so satisfactory, for a little bromine is formed and the final product has an orange color instead of a clear yellow.   Under the conditions specified, the reaction proceeds satisfactorily and smoothly.   If the temperature does not rise spontaneously in a few minutes to 75°, some mistake has been made.   The most probable one is the addition of too little acid.

4. Measure the initial and final temperatures as accurately as convenient, in order to calculate ΔH for the reaction (see Question 11).   The radiation loss may be approximated by observing the rate of cooling of a flask of water under similar conditions.

5. Quinone has an appreciable vapor pressure at the ordinary temperature and is readily volatile with steam.   On this account it is desirable to carry out the operation in a flask, to heat the solution rapidly and not allow the temperature to rise much above 80°.   Besides, at 80° and higher temperatures the liquid sometimes becomes cloudy, probably owing to the formation of bromoquinone from excess bromate.

6. If heating is continued too long, the liquid becomes cloudy.   When this happens, filtration while hot is necessary.   Precautions to prevent cooling should be taken.

7. The moist solid slowly turns dark.   The yield is 90%.   Quinone melts at 116°.

8. This experiment is based on work by H. N. McCoy, *Jour. Chem. Ed.*, **14**, 494 (1937).

Questions

1. Why does the temperature become too high merely because larger quantities are used?

2. What is the approximate concentration of sulfuric acid in the reaction mixture?

3. Would you conclude that sulfuric acid catalyzes the reaction or merely serves to liberate bromine slowly?   Explain.

4. To what is the initial dark color due?

5. Write the equation for the formation of bromine, and describe the effect of hydrogen-ion concentration on its rate of formation.

6. Why is the presence of bromine undesirable?

7. At what point is the rate of formation of bromine greatest?

8. Assuming a quantitative conversion of hydroquinone to quinone, calculate the approximate solubility of quinone in water at 0°, from the yield.

9. What other reagents may be used for oxidizing hydroquinone to quinone?

10. Can quinone be obtained from other organic compounds? Explain.

11. Calculate an approximate ΔH for this reaction. Is it positive or negative?

12. Calculate the equilibrium constant for the reaction of bromate and hydroquinone.

Experiment 38–2   Preparation of 1,4-Naphthoquinone (Note 1)

Equip a suitable flask (500-ml.) with a mechanical stirrer (Note 2) and a dropping funnel which can be attached later. In the flask prepare a fine loose suspension of 0.10 mole of naphthalene in a mixture of 100 to 150 ml. of glacial acetic acid, 10 ml. of water (Note 3), and 5 g. of concentrated sulfuric acid (Note 4) by heating the mixture until the naphthalene is dissolved, and then cooling rapidly under the tap with agitation, taking care that the naphthalene does not separate first as an oil (Note 5) and does not stick to the glass. In case much sticks to the upper part of the flask, playing a flame carefully on the outside will cause it to flow down. Prepare also a solution of 0.5 mole of chromic anhydride (Notes 6 and 7) in 35 g. of hot water (Note 8). Cool, and add to this 30 ml. of glacial acetic acid and 5 g. of concentrated sulfuric acid. Add this solution to the naphthalene suspension during the course of 0.5 hour.

Stir vigorously, and keep the temperature at 25° by means of an ice-cold bath. As the last of the solution is added, only moderate cooling is necessary, as with a bath at 15° or 20°. During the next operation of testing, allow the temperature to rise to 35° or even 40°. This promotes the oxidation of the last of the naphthalene (Note 6).

As soon as the oxidizing solution has been added, at once remove a small portion of the reaction mixture, add it to twice the volume of water, and mix thoroughly. Collect the solid by suction filtration on a small funnel, wash it a few times with dilute acetic acid (2 N or 3 N; Note 9), and wash out the acid with water. If the color of the solid is orange, orange-green, or greenish yellow, continue the stirring while the temperature is maintained at 30° to 35°. Test every few minutes. This final period should require about 1 to 10 minutes. If a longer time is required, the yield is low. Just as soon as the solid is bright yellow in color and has no odor of naphthalene (Note 10), quench the reaction by pouring the mixture slowly into 0.5 liter of water (Note 11) while stirring mechanically.

Continue the stirring for at least 0.5 hour (Note 12). Collect the solid by suction filtration. Wash several times with small amounts of dilute acetic acid (2 N or 3 N) until free of sulfuric acid and chromium com-

pounds and then with water until free of acetic acid.   Dry the solid *completely* and as rapidly as possible (Note 13).   Determine the melting point, and calculate the percentage yield (Note 14).

Notes

1. The oxidation of β-methylnaphthalene to β-methyl-1,4-naphthoquinone (m.p. 105–106°) may be carried out in much the same manner, except that the amount of acetic acid should be 150 ml.   Under these conditions any undissolved part of the hydrocarbon is an oil.

2. This need not be a sealed stirrer.

3. In the absence of water a heavy sludge appears when the chromic anhydride solution is added.   The reaction proceeds more smoothly when water is present, since the amount of sludge is decreased.   When also a larger amount of acetic acid is used, sludge formation decreases further, and the product is purer, but the yield is somewhat lower.

4. In the absence of sulfuric acid the oxidation of naphthalene to naphthoquinone requires about 70 hours, and the yield is about 30%.   In the procedure as described, the reaction is so accelerated by the added sulfuric acid that oxidation is complete in a reasonable time, and the end of the reaction can be detected readily.   With less acid the oxidation proceeds more slowly.

5. Oil formation is not serious, as long as the drops are finely divided.   To be avoided is solidification of the oil, forming clumps of solid.   These react slowly.

6. A large excess of chromium trioxide is necessary; otherwise, some naphthalene remains unoxidized.   Oxidation of some of the quinone also takes place.   This reduces a larger amount of the trioxide, per mole of reductant.   Best yields result if the naphthalene is oxidized completely during the addition of the oxidizing agent.   For this reason the naphthalene should be properly prepared.

7. The technical grade thin flakes are satisfactory, if a dilute aqueous solution is clear and has the characteristic dichromate color.

8. Water serves a double purpose.   It dissolves the anhydride readily and diminishes its oxidizing action on the quinone.

9. Centrifuging is satisfactory but not so rapid as filtration.

10. A bright-yellow color indicates that the solid is essentially pure 1,4-naphthoquinone.   In case the solid is greenish or orange in color and/or has an odor of naphthalene, as well as of quinone, the oxidation is incomplete.   The solid may be purified by crystallization, although with considerable loss, from alcohol, ether, ligroin (80–120°), or preferably low-boiling petroleum ether.   It is better to carry out the oxidation properly and not rely on crystallization.

11. If the amount of water is too small, the product is less pure; if too large, some quinone is lost, owing to its slight solubility.   Add some dilute acetic acid to the residue in the flask.   Combine the resulting mixture with the main portion only if the purity of the solid is satisfactory.

12. Stirring is desirable in causing the amorphous precipitate to become crystalline.   This aids filtration and increases the purity of the final product.

13. *Caution:* The compound is slightly volatile at room temperature and turns dark in the moist condition.   Remove as much water as possible by absorption (pressing between absorbent paper or on porous tile), and then spread thinly to facilitate final drying in the air.

14. The melting points of pure 1,4-naphthoquinone and β-methyl-1,4-naphthoquinone are 125° and 105–106°, respectively. The yields of products melting at 123–124° and 103–104°, respectively, are 70%.

Questions

1. What is the excess of chromic anhydride over the theoretical, in per cent?
2. Explain why this excess must be large.
3. Why is the oxidizing power diminished by the addition of water?
4. What products are formed when the naphthoquinone undergoes oxidation?
5. Why is dilute acetic used in the first wash rather than water?
6. From what compound is 1,4-naphthoquinone formed by the action of ferric chloride?
7. Which is the stronger oxidizing agent: 1,4-benzoquinone or 1,4-naphthoquinone?
8. Can you give a reason for your answer to 7?

Experiment 38–3   Preparation of 2-Bromoanthraquinone

To 0.05 mole of 2-(4'-bromobenzoyl)benzoic acid in a round-bottomed 1-liter flask (Note 1) add 100 g. of ordinary technical concentrated sulfuric acid (Note 2). Mix well, and heat for 2 hours in an oil bath maintained at a temperature of 150°. Allow to cool. Precipitate bromoanthraquinone by the slow addition (Note 3) of 1 liter of water (Note 4) with shaking and cooling if necessary under the tap. Collect the product by suction filtration, and remove acidic impurities by extracting with a few milliliters of concentrated aqueous ammonia until the washings are no longer highly colored. Press out on porous plate, and let stand until reasonably dry.

Purify the *completely dried* material (Note 5) by sublimation at reduced pressure (Chapter 11).

Notes

1. A smaller flask could be used, but this would necessitate transference later. However, the small flask has one advantage in that the mixture can be heated with the direct flame. In this case the thermometer bulb is placed in the liquid.
2. The yield drops off with a decrease in the amount of acid.
3. The product is purer if water is added to the acid, rather than the reverse. At first, add only 1 or 2 ml. at a time (*Caution*).
4. By the cautious addition of only 10 to 12 ml. of water to the sulfuric acid, the impurities largely remain in solution, whereas the quinone separates. However, filtration of a mixture of such concentrated acid is troublesome. In such case a sintered glass funnel is useful. The product so obtained is yellow pure crystals which melt at 205°. The yield is 35%.

Addition of a large volume of water to the filtrate throws down impure bromo-anthraquinone, which is collected as described above. This may be purified by sublimation or by dissolving in sulfuric acid and repeating the process.

The sintered glass funnel should be freed of sulfuric acid by many washings, first with water, then with ammonia, finally with water.

5. Final drying may be done in an oven at 105–110°, but not higher, since bromo-anthraquinone begins to sublime at these temperatures. The melting point is 205°, and the yield of sublimed product is 70 to 80%.

Questions

1. How is 2-(4'-bromobenzoyl)benzoic acid prepared?
2. Can you advance any reason for the decreased yield with a smaller amount of sulfuric acid?
3. Can you advance any reason for a higher purity when less water is added to the reaction mixture? What are the impurities?
4. What type of compounds are removed by the ammonium hydroxide?
5. How many monobromo-9,10-anthraquinones are possible?
6. How many dibromo-9,10-anthraquinones?

Experiment 38–4   Properties of Quinones

Use 2 or 3 ml. of an aqueous saturated solution of benzoquinone in each of the tests described here, with the exception of B3.

A   QUINHYDRONE FORMATION.   Add 1 to 2 ml. of an aqueous solution of hydroquinone and shake well. Describe the results.

B   REDUCTION.   1. Add drop by drop a dilute (5% or *less*) solution of sodium bisulfite until there is no further change (Note 1). Describe the results.

2. Add 1 to 2 ml. each of dilute sulfuric acid and aqueous potassium iodide. Describe the results.

3. To about 0.1 g. of β-bromoanthraquinone dissolved in a minimum quantity of warm alcohol, add some zinc dust and 1 to 2 ml. of 6 N sodium hydroxide. Keep warm for a few minutes. Decant some of the solution onto a watch glass. Describe the results.

C   OXIDATION.   1. Add a few drops of aqueous sulfuric acid followed by a few drops of aqueous permanganate. Repeat, using sodium car-bonate instead of sulfuric acid. Describe the results.

2. Add a few drops of aqueous sodium (or potassium) dichromate and dilute sulfuric acid. Describe the results.

Notes

1. If a saturated or concentrated solution is used, an excess of bisulfite may be present with the first drop, and thus the intermediate step will not appear.

Questions

1. Is hydroquinone easily oxidized?
2. Is quinone easily reduced?
3. What is quinhydrone?
4. Why is it of interest from a physicochemical point of view?
5. Write balanced equations for the reactions that take place in these experiments.
6. What are the equilibrium constants in B1, 2, and 3?
7. Name four other reducing agents which will reduce β-bromoanthraquinone.
8. Under which conditions of hydrogen-ion concentration will ferric ion oxidize hydroquinone, and under which conditions will ferrous ion reduce quinone (Table 1–4)?
9. What is the composition of the equilibrium mixture obtained when equimolar amounts of p-benzoquinone and 9,10-anthracenediol are dissolved in alcohol?

Chapter 39

DIPHENYLMETHANE AND TRIPHENYLMETHANE COMPOUNDS

Diphenylmethane and triphenylmethane compounds result from a variety of condensation reactions, such as (a) the Friedel–Crafts synthesis, (b) the condensation of aromatic alcohols with aromatic compounds, (c) the condensation of phthalic anhydride with phenols, (d) the condensation of aldehydes and ketones with aromatic compounds, especially with phenols and tertiary amines, (e) the condensation of two or more aromatic amines, one of which has a methyl side chain, by the action of a mild oxidizing agent:

(a)
$$CH_2Cl_2 + 2C_6H_6 \xrightarrow{AlCl_3} C_6H_5CH_2C_6H_5 + 2HCl$$

$$C_6H_5CH_2Cl + C_6H_6 \xrightarrow{AlCl_3} C_6H_5CH_2C_6H_5 + HCl$$

$$CHCl_3 + 3C_6H_6 \xrightarrow{AlCl_3} C_6H_5CH(C_6H_5)_2 + 3HCl$$

$$CCl_4 + 3C_6H_6 \xrightarrow{AlCl_3} C_6H_5CCl(C_6H_5)_2 + 3HCl$$

$$C_6H_5CHCl_2 + 2C_6H_6 \xrightarrow{AlCl_3} C_6H_5CH(C_6H_5)_2 + 2HCl$$

(b)
$$C_6H_5CH_2OH + C_6H_6 \xrightarrow{H_2SO_4} C_6H_5CH_2C_6H_5 + H_2O$$

$$(C_6H_5)_2CHOH + C_6H_6 \xrightarrow{H_2SO_4} C_6H_5CH(C_6H_5)_2 + H_2O$$

(c)

phenolphthalein

(d)
$$H_2C(OCH_3)_2 + 2C_6H_6 \xrightarrow{H_2SO_4} C_6H_5CH_2C_6H_5 + 2CH_3OH$$

$$C_6H_5CHO + 2C_6H_5OH \xrightarrow{ZnCl_2} C_6H_5CH(C_6H_4OH)_2 + H_2O$$

$$C_6H_5CHO + 2\,C_6H_5NMe_2 \xrightarrow{ZnCl_2} C_6H_5CH(C_6H_4NMe_2)_2 + H_2O$$

$$(C_6H_5)_2CO + C_6H_5NMe_2 \xrightarrow{ZnCl_2} (C_6H_5)_2C(OH)C_6H_4NMe_2$$

(e) $p\text{-}NH_2C_6H_4CH_3 + 2HC_6H_4NH_2 + 3H_3AsO_4 + HCl \rightarrow$

$$(H_2NC_6H_4)_2C{=}C_6H_4{=}\overset{+}{N}H_2 + \overset{-}{Cl} + 3H_2O + 3H_3AsO_3$$

39.11   The Friedel–Crafts Condensation (method *a*). This reaction is discussed in 29.13 and in 36.16.   Diphenylmethane, triphenylmethane, or derivatives of these can be prepared readily by the action of the corresponding halogenated methane with aromatic compounds. Thus, from benzene the product with methylene chloride is diphenylmethane, and with chloroform it is triphenylmethane (tritane).   However, with carbon tetrachloride the product is triphenylchloromethane (trityl chloride, Experiment 39–1), even when a large excess of benzene is taken.   (If carbon tetrachloride is in excess, the product is diphenyldichloromethane, largely, and some benzotrichloride.)   The recovery of the product, if a hydrocarbon, is easy, but in the case of triphenylchloromethane it is complicated by the ready hydrolysis of the product at room temperature to triphenylcarbinol.   This compound can be reconverted to the chloride by warming with acetyl chloride.

$$(C_6H_5)_3CCl + H_2O \rightarrow (C_6H_5)_3COH + HCl$$

$$(C_6H_5)_3COH + CH_3COCl \rightarrow (C_6H_5)_3CCl + CH_3COOH$$
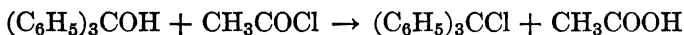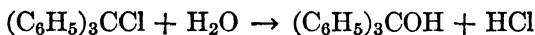
39.12   Condensation with Oxygenated Compounds.   Reactions *b*, *c*, and *d* require elevated temperatures and the presence of a suitable catalyst, as for example concentrated sulfuric acid, anhydrous zinc chloride, anhydrous stannic chloride, or anhydrous aluminum chloride. Sulfuric acid, although it is an excellent catalyst and is effective in small amounts, suffers from the disadvantage of sometimes sulfonating some of the materials or of causing charring, or resinification (as with benzyl alcohol).   Anhydrous zinc chloride, although less effective catalytically than sulfuric acid, does not possess these disadvantages.   It is much used, since it is not expensive.   Anhydrous stannic chloride has the advantage of being a liquid in which the reactants usually are soluble. However, larger amounts must be taken, and purification of the product is more difficult.   Aluminum chloride may catalyze other reactions and thus lead to only low yields of the desired products.

Aromatic hydrocarbons will condense with alcohols, acid anhydrides, aldehydes, and ketones, but the reactions are quite slow, even with a catalyst at elevated temperatures.   The reaction with aliphatic compounds usually is not so satisfactory as with aromatic oxygenated com-

pounds, for the latter have much higher boiling points. Thus benzene yields diphenylmethane (I) with benzyl alcohol; triphenylmethane (II) with benzaldehyde; triphenylcarbinol (III) with benzophenone; and diphenylphthalide (lactone of carboxytriphenylcarbinol) (IV) with phthalic anhydride, as the following formulas show:

$$C_6H_5CH_2OH$$

$$\downarrow$$

$$C_6H_5CH_2C_6H_5$$

I

$$(C_6H_5)_2C=O$$

$$\downarrow$$

$$(C_6H_5)_2C(OH)C_6H_5$$

III

$$C_6H_5CHO$$

$$\downarrow$$

$$C_6H_5CH(C_6H_5)_2$$

II

$$\begin{array}{c} C_6H_4\text{---}C=O \\ | \quad\quad | \\ O=C\text{---}O \end{array}$$

$$\downarrow$$

$$\begin{array}{c} C_6H_4\text{---}C(C_6H_5)_2 \\ | \quad\quad\quad | \\ O=C\text{---}O \end{array}$$

IV
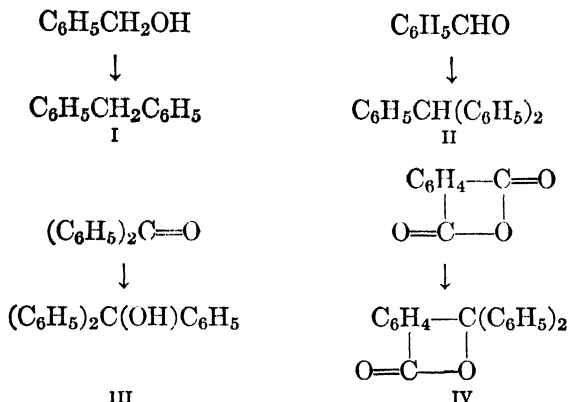
These compounds are all colorless, and remain so on the addition of dilute aqueous acids or bases.

Phenols and tertiary amines of the dimethylaniline type are much more reactive than aromatic hydrocarbons, but even then temperatures of 150° to 180° usually are necessary. The reactions take place at the *para* position, and, if this is occupied, at the *ortho* position. The products are acidic if phenol is one of the reactants, and basic if dimethylaniline is a reactant. The important compounds are those related to triphenylmethane, that is, those resulting from the action of benzaldehyde, benzophenone, phthalic anhydride, or related compounds, because of their importance as sources of highly colored compounds. Type III compounds become intensely colored on the addition of dilute base if acidic phenolic groups are present: or on the addition of dilute acid if basic amino or substituted amino groups are present, if these groups occupy *ortho* or *para* positions. Such compounds are called color bases in the latter case. Type IV compounds, if phenolic groups are present (phenolphthalein for example), become highly colored on the addition of dilute base.

The condensation product of phthalic anhydride with resorcinol is not a simple hydroxy phthalide, like phenolphthalein, for water is eliminated between two hydroxyl groups, forming a pyrone ring. The product, fluorescein (Experiment 39-3), is colored, even in the absence of a base.

fluorescein
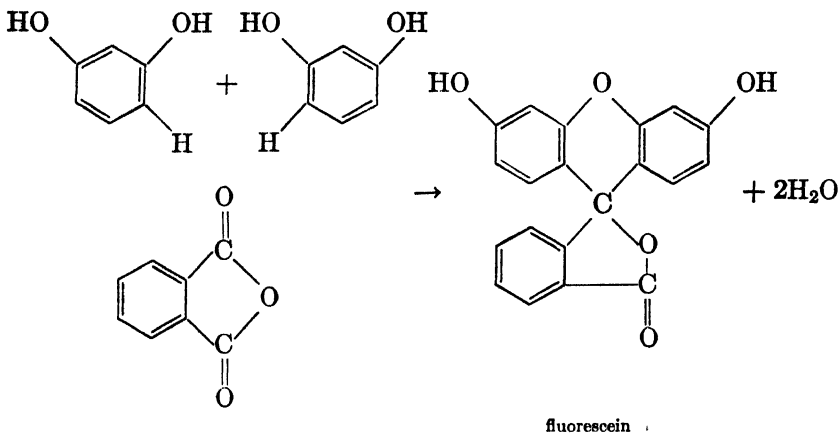
39.13   Oxidation of Leuco Bases. A typical leuco base (an amine which can be oxidized to a color base) is tetramethyldiaminotriphenylmethane (V), and a typical color base is tetramethyldiaminotriphenylcarbinol (VI). These are formed in the preparation of malachite green (Experiment 39–2).

$$C_6H_5CH[C_6H_4N(CH_3)_2]_2 + PbO_2 + 2HCl \rightarrow$$
$$V$$

$$C_6H_5C(OH)[C_6H_4N(CH_3)_2]_2 + PbCl_2 + H_2O$$
$$VI$$
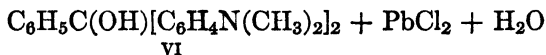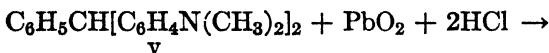
The conversion of V to VI is essentially the oxidation of a side chain. The oxidation must not be too vigorous, since, otherwise, one or more of the benzene rings may be attacked. Also the oxidizing agent should be one that is easily removed from the product. Lead peroxide is one of the best reagents for this reaction. As the color base is formed, it is converted to the dye, malachite green.

$$C_6H_5C(OH)[C_6H_4N(CH_3)_2]_2 + HCl \rightarrow$$

malachite green
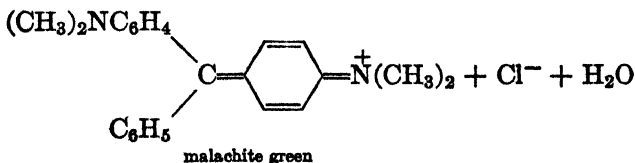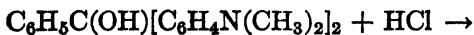
39.14   Condensation by Mild Oxidation. In method *e* dyes of the triphenylmethane type often can be obtained directly by the action of an oxidizing agent on aromatic amines in acid solution. The color

base is formed by the action of the oxidizing agent and then is converted into the dye by the acid present.

. It is essential that at least one third of the amines present have a methyl side chain. The oxidizing agent should be a mild one, for example arsenic acid or a nitro compound such as nitrobenzene. Vigorous oxidizing agents may bring about other changes; for example, chromic acid may convert the amine to a quinone, and permanganate will cause destruction of aromatic character. For these mild oxidations a nitro compound has the advantage over arsenic acid that it is more economical, and the reduction product, the amine, can react in the condensation. For this reason the nitro compound must be selected so as to give the desired amine.

Experiment 39–1   Preparation of Triphenylchloromethane
(Trityl Chloride)

Equip a dry two-necked-flask with a dry reflux condenser, and to this connect a device for absorbing the evolved hydrogen chloride without danger of water being drawn into the apparatus. The connections should be tight to prevent escape of hydrogen chloride and also to prevent entrance of water, in case heating is done later by a steam or hot-water bath. Add to a mixture of 0.10 mole of carbon tetrachloride and about 1.5 mole of pure benzene, both free of water (Notes 1 and 2), 0.15 mole of finely divided anhydrous aluminum chloride (as AlCl₃, Note 3) in several portions. *Shake frequently.* Finally, after the evolution of hydrogen chloride has moderated, by means of a bath heat at refluxing temperature for 1 hour, or until hydrogen chloride ceases to be evolved. If the liquid darkens stop the heating, for removal of color from the product is not easy. Cool, pour the reaction mixture slowly in a fine stream into a mixture of ice and hydrochloric acid, and with vigorous agitation or stirring completely decompose addition compounds so that all aluminum is extracted from the organic phase (Note 4). In case the benzene freezes, add some other solvent to it, for example toluene. Work rapidly, to minimize hydrolysis of the desired product. Add more solvent in case a solid crystallizes from solution.

Remove any ice, separate the phases, and wash a few times with cold dilute hydrochloric acid and finally with water. Remove water thoroughly and as rapidly as possible with a suitable drying agent. Test a small portion of the liquid for aluminum chloride by shaking it thoroughly with dilute hydrochloric acid, separating the phases, and making the aqueous phase basic with ammonia. In case the test indicates that much aluminum chloride is present, repeat the washing process on the

benzene solution. Filter the anhydrous liquid if not clear. Distil off the solvent (Note 5) until a small portion of the liquid solidifies on cooling. Cool, add an equimolar portion of acetyl chloride (Note 6), warm to dissolve the solid (Note 7), filter if not clear, and transfer to a small flask for crystallization, avoiding contact with moisture of the air from this point on.

Collect rapidly by suction filtration, protecting the solid by a rubber dam (refer to Subsection 5.41). Dry overnight in a desiccator, preferably a vacuum desiccator, in which caustic flakes and paraffin shavings are present in separate small dishes (refer to Subsection 5.43). From the filtrate additional solid may be recovered by removing most of the solvent by evaporation under reduced pressure.

If the product is impure (Notes 8 and 9), purify by crystallizing from a small amount of acetyl chloride, as previously, adding some benzene if necessary.

Notes

1. Let each stand overnight with anhydrous calcium chloride, which should be removed before starting the experiment.

2. Only about 0.6 mole of benzene is necessary here, and this amount of dry benzene gives satisfactory results. The rest is needed later to act as a solvent. This need not be anhydrous.

3. Exposure to moisture soon renders the anhydrous form useless for this experiment.

4. In case a mechanical stirrer is not available, vigorous shaking in a bottle or flask not over half full is recommended; otherwise, the aluminum addition compounds are not decomposed completely.

5. Do not overheat towards the end. An oil or wax bath may be used.

6. Thionyl chloride may be used in place of acetyl chloride. However, it reacts more slowly. This operation should be carried out in the fume hood.

7. In case the solid does not dissolve completely on heating, a little benzene may be added, and heat applied. However, do not confuse product with solid impurities.

8. Washing with a *small* amount of dry ether removes some impurities. However, the product is somewhat soluble in ether.

9. Triphenylchloromethane melts at 111°. Yield is 75 to 80%.

Questions

1. What would happen if an attempt were made to drive water out of aluminum chloride hexahydrate by heating strongly?

2. How can one determine quantitatively the fraction of a given sample of aluminum chloride that is anhydrous?

3. Is there enough benzene to react with the fourth chlorine atom of carbon tetrachloride?

4. Why is an excess of benzene taken?

5. Why is toluene added?

6. What undesirable side reaction may take place when the reaction mixture is poured into water?

7. Why is it better to distil off and recover benzene rather than evaporate?

8. Why is acetyl chloride used for crystallization?

9. What is the main impurity in the product?

Experiment 39–2   Preparation of Malachite Green (Note 1)

PREPARATION OF THE LEUCO BASE. In a 1-liter or 2-liter two-necked flask (Note 2) heat 0.10 mole of recently distilled benzaldehyde (Note 3), 0.15 mole of recently fused anhydrous zinc chloride (Note 4), and a 10 to 20% excess of dimethylaniline. Heat by means of an oil or wax bath at 100° to 110° for about 0.5 hour, mixing frequently so that the zinc chloride will be well dispersed. Maintain at 100–110° for several hours (Note 5) or until a small test portion of the mixture fails to show the presence of benzaldehyde (Note 6).

Steam-distil until the odor of dimethylaniline is no longer evident and oil no longer comes over. Cool the flask and contents, pour off the aqueous phase, wash the viscous residue of leuco base several times with water, and wash once, quickly, with *cold* ethyl alcohol.

Crystallize from a liberal amount of alcohol (Note 7; refer to 5.22). Crystallization usually is better if alcohol is not too hot, not over 60°. Take particular care to prevent formation of oil (refer to 5.33), which is usually observed in this case, owing to slowness of the crystallization process and large temperature coefficient of solubility in the warm solvent. Promote crystallization by scratching and/or seeding. After crystallization has started, see that the temperature drops only very slowly. Let stand overnight or longer. The presence of a hard cake shows that oil had separated. In such case repeat the crystallization. Collect the solid by suction filtration, and, before washing it, remove the filtrate. Discard the washings. Cool the filtrate in a good freezing mixture, or let stand 1 or 2 days in a cold place, to obtain a second crop. Remove solvent rapidly from the solid by absorption, to minimize development of color, which usually follows exposure to air while solvent is present. When it is *completely free* of solvent, take the melting point of each crop, and determine the percentage yield (Note 8). Recrystallize from alcohol if the melting point is low by more than 4°.

OXIDATION OF THE LEUCO BASE. To 0.010 mole of the dry, finely divided leuco base add an excess (20 to 30%) of hydrochloric acid over the amount required for the oxidation and for the formation of the dye salt. Add enough water to bring the volume to 50 to 100 ml., heat to 50° or 60° if necessary, and stir until the leuco base has been converted

to the soluble salt.   Dilute to about 0.3 liter, add ice to bring the temperature to near 0°, and filter if the solution is not clear (Note 9).

To the cold solution, about 0.5 liter, preferably in a large beaker, add gradually, with continuous stirring and over a period of 15 to 30 minutes, an excess (about 25%) of hypochlorite-free lead dioxide in the form of a thin paste with water (Note 10). Stir for 1.5 to 2 hours. After the solution has stood quiet for several minutes, examine the vessel for insoluble material by carefully pouring out the liquid.   If there is any residue, add some water, acidulated with a drop of hydrochloric acid, to determine if the residue is dye, leuco base, or a lead compound. Filter the solution in case a residue was noted.   If desired, any lead in solution can be precipitated at this point as lead sulfate by the addition of a small excess of sodium sulfate.

To the dark green aqueous solution of the dye add the following clear aqueous solutions: (1) about 0.03 mole of zinc chloride; (2) saturated sodium chloride (Note 11).   Add the latter slowly with stirring, and stop as soon as solid begins to separate, revealed by the presence of dark spots on the surface of the liquid or by stationary dark spots on filter paper when a drop is added to the paper.   Continue with slow addition of salt until most of the dye has separated.   Test by adding a drop to filter paper.   Let stand for some time, preferably over night. Collect by suction filtration on a small filter.

Dissolve the still moist residue by adding to the solid, in a beaker, 0.2 to 0.3 liter of acidulated water at about 80°, stirring well.   Note that only a few drops of acid are necessary to prevent hydrolysis of zinc chloride.   Decant off the solution through a filter, and add more acidulated hot water to the residue.   Repeat if necessary.   The dye should dissolve in 0.4 to 0.6 liter.   To the cold solution add a little zinc chloride (only a fraction of the previous amount).   Precipitate with sodium chloride, as before.

Collect by suction filtration, wash with ice-cold water from a dropper, dry to constant weight, and determine the percentage yield (Note 12).

Notes

1. Special care must be exercised to avoid spilling any of the solutions, even if it is not highly colored, because removal of the resulting stains from desks, sinks, and other surfaces is difficult.   Therefore, when discarding any liquids in this experiment, *pour them carefully down the drain pipes; do not dump them into the sinks.*   In suction filtration use glass funnels holding filter plates instead of using Buechner or Hirsch funnels.   It is very difficult to remove the dye stain from the inside of these funnels.

2. Mechanical agitation is preferred but is not necessary.   However, frequent mixing is desirable, owing to the slow dissolving of the solid.   Because steam distillation is to be performed later, a large two-necked flask is preferred.

3. Benzaldehyde by itself is rapidly oxidized by air.

4. The amount to be taken is not critical and may be more or less than that specified. After fusing the zinc chloride in a porcelain or iron crucible, reduce it to small granules quickly in a mortar. Do not allow it to stand in moist air but use immediately.

5. It has been observed that heating time can be decreased if the temperature is higher, for example, 0.5 hour at 150° in place of additional heating at 100–110°. However, the product then may be more difficult to crystallize, probably owing to impurities from side reactions.

6. Note that the odor of dimethylaniline masks that of benzaldehyde. Devise a method of testing that will overcome this difficulty. Consult instructor if in doubt.

7. Sometimes, especially when the reaction has been carried out at higher temperatures, a residue insoluble in alcohol has been encountered. This may be a basic zinc compound.

8. There are two forms of the leuco base, namely, needles (m.p. 102°) and leaflets (m.p. 93–94°). Yield is 80%.

9. The solution usually has a green color, even though the leuco base seemed colorless. The color is not significant. The volume of the solution needs to be large; otherwise, a solid may precipitate during the oxidation.

10. A freshly prepared sample of lead dioxide is recommended, owing to the fact that the reactivity decreases with age, especially with drying. This effect probably is related to the particle size.

In a beaker or large flask add to an aqueous solution of the desired amount of lead acetate or lead nitrate an amount of sodium hydroxide (usually 5 to 8 equivalents) sufficient to redissolve most of the precipitate first formed. Pass in chlorine gas through a glass tube having an opening of about 1 mm., so as to obtain reasonably small bubbles. Agitate continuously, keep the temperature below 50° to 60°, and test for completion of reaction by passing chlorine through a filtered test solution. In case the reaction mixture becomes thick, add more water. Centrifuge, and wash the dark brown (almost black) solid several times with water, centrifuging each time, until it is free of hypochlorite.

In case chlorine is not available, use a dilute solution of bleaching powder. Test this, to be sure it is fresh.

11. Clean salt may be added after precipitation has started instead of aqueous sodium chloride, to avoid an excessively large volume.

12. The product is a double salt of the dye with zinc chloride. The formula is $3C_{23}H_{25}N_2Cl \cdot 2ZnCl_2 \cdot 2H_2O$. Yield in this step, 55–60%.

Questions

1. What is the usual contaminant of old specimens of benzaldehyde?
2. What is the main component of the oil that steam-distils?
3. What is the formula of the leuco base?
4. Why is it called a leuco base?
5. Why is it washed with water?
6. Why is it washed with alcohol?
7. Why is the alcohol kept cold?
8. Why is the crystallization process slow?
9. In the preparation of lead dioxide, why is the excess of sodium hydroxide so large?

10. What white precipitate is formed when sodium hydroxide is first added to the solution of the lead salt?

11. What is formed when this precipitate dissolves on the addition of more base?

12. What is the effect of heat on sodium hypochlorite?

13. Write equations for the reactions involved in the preparation of lead dioxide.

14. Write equation for the oxidation with lead dioxide.

15. What are the main contaminants of the first dye precipitate?

16. Which of these are largely removed by dissolving and reprecipitating?

17. What is formed when sodium hydroxide is added to a solution of malachite green?

18. What product do you predict would be formed by adding 1, 2, 3, or 4 molecules of bromine to an anhydrous solution of the leuco base?

19. What product do you predict would be formed by the action of metallic zinc on a solution of malachite green in glacial acetic acid?

20. Show how malachite green can be prepared by other condensation reactions.

Experiment 39–3   Preparation of Fluorescein (Notes 1 and 2)

In a mortar grind together 0.02 mole of phthalic anhydride with a 20% excess of resorcinol, and place the mixture in a vessel from which the solid reaction product later can be removed readily and which can be heated conveniently in an oil bath (Note 3). Heat to 180°, add to the molten mixture about 0.02 mole of anhydrous zinc chloride (Notes 4, 5, and 6), and mix well by stirring. Maintain a temperature of 180° until the mass solidifies (Note 7).

Cool, grind the solid to a fine powder, and boil for several minutes with 50 or 75 ml. of dilute (about 1 N) hydrochloric acid (Note 8). Collect by suction filtration, wash, dry, and calculate the percentage yield.

Purify the product further by dissolving it in cold dilute (about 0.2 N) sodium hydroxide, filtering and acidifying with hydrochloric acid. Filter as before, and dry the product *completely*. Determine the per cent recovery for this operation (Note 9). Label this "purified by precipitation."

Notes

1. This is a general procedure for condensing phthalic anhydride with phenols. Monohydric phenols yield phthaleins. In such cases, some excess of the phenol is desirable.

2. Special care must be exercised to avoid spilling any of the solutions, because removal of the resulting stains from desks, sinks, and other surfaces is difficult. Therefore, any of these solutions to be discarded must be *poured carefully down the drain pipes, not dumped into the sinks*. In suction filtration Buechner or Hirsch funnels should not be used, because of the difficulty of removing the dye stain from the inside. Instead, glass funnels holding filter plates should be substituted.

3. A porcelain, nickel, or iron dish or crucible is satisfactory.

4. The amount is not critical; more or less may be taken.

5. Technical zinc chloride powder is satisfactory. Some authors recommend heating it beforehand to drive out water. There is some doubt about the necessity of doing this.

6. Other condensing agents may be used also, for example anhydrous aluminum chloride and, with poorer results, anhydrous ferric chloride. The reaction is catalyzed also by sulfuric acid, but again with poor yields.

7. If the mass has not solidified after 1 hour, the temperature may be raised to 210°, and the heating continued.

8. The acid is added to dissolve zinc oxide and/or basic zinc chloride.

9. In case the material is colloidal in character and does not settle well after acidification, heating the mixture and adding an excess of acid to the hot solution often aids coagulation. Yield, essentially quantitative.

Questions

1. Why should some excess of a monohydric phenol be taken when a phthalein is to be prepared?

2. What is the product when phthalic anhydride, benzene, and anhydrous aluminum chloride are gently heated (to 90° or 95°, but not higher)?

3. What happens when moist zinc chloride is strongly heated?

4. Why are zinc oxide and basic zinc chloride liable to be present?

5. What is the principal impurity in the crude reaction product?

6. What impurity or impurities are removed by filtering the sodium hydroxide solution?

7. What is the principal impurity of the reprecipitated product?

8. What reaction takes place when fluorescein dissolves in sodium hydroxide solution? Equation.

Experiment 39–4   Properties of Triphenylmethane Compounds

A   REACTIVITY OF TRITYL CHLORIDE.   Compare the rate of reaction of alcoholic silver nitrate with *n*-butyl chloride, benzyl chloride, and triphenylchloromethane.

B   FREE RADICAL FORMATION.   In a well-stoppered homeo vial shake dry benzene (Note 1), a small amount of triphenylchloromethane, and some zinc dust. Pour some of the resultant solution into an open dish (small beaker).

C   REDUCTION OF A DYE TO THE LEUCO BASE.   To very dilute solutions of malachite green add a few drops of hydrochloric acid and separately: (*a*) dilute sodium hydrosulfite solution, (*b*) a pinch of zinc dust (or granulated zinc) (see Experiment 39–2, Note 1).

D   MALACHITE GREEN, ACID AND ALKALI.   To dilute solutions of malachite green slowly add separately (*a*) concentrated hydrochloric acid, (*b*) sodium hydroxide solution. Neutralize each solution.

E   PHENOLPHTHALEIN, ACID AND ALKALI.   Repeat D, but use a large excess of sodium hydroxide in (*b*).

Notes

1. Thoroughly dried by shaking with calcium chloride.

Questions

1. How do you account for the order of reactivity of the chlorides tested?
2. Write equations for the reactions which take place in the first and second parts of B.
3. Write equations for the reactions in C, D, and E.
4. Does the relation between the concentration of hexaphenylethane in benzene solution and the intensity of the color of the solution follow Beer's law?

MALONIC ESTER AND ACETOACETIC ESTER

Malonic ester (ethyl malonate) is important in the preparation of carboxylic acids, and acetoacetic ester (ethyl acetoacetate) is important in the preparation of both ketones and carboxylic acids.

The great usefulness of these esters which are available commercially lies in the fact that they form sodium salts which can react with an organic halide or certain other organic compounds to give, respectively, a monosubstituted malonic or acetoacetic ester. From the monosubstituted ester a sodium salt can be prepared, and this in turn can react with a second organic halide to give a disubstituted ester.

The substituted esters yield other products. Saponification can be carried out so that from the substituted malonic esters the respective malonic acids or substituted acetic acids can be obtained, and from the substituted acetoacetic esters substituted acetoacetic acids, acetones, or acetic acids can be obtained.

Typical ester syntheses using sodioesters, prepared in anhydrous alcoholic solution by the action of sodium ethoxide on acetoacetic ester or malonic ester are the following: (a) *n*-butylacetoacetic ester, (b) di-*n*-butylacetoacetic ester, (c) methylmalonic ester, and (d) methyl-*n*-butyl-malonic ester.

(a)
$$Na + EtOH \rightarrow EtONa + \tfrac{1}{2}H_2$$

$$EtONa + CH_3\underset{\underset{O}{\|}}{C}CH_2COOEt \rightarrow CH_3C\underset{\underset{ONa}{|}}{=}CHCOOEt + EtOH$$

$$n\text{-}C_4H_9Br + CH_3\underset{\underset{ONa}{|}}{C}=CHCOOEt \rightarrow CH_3\underset{\underset{O}{\|}}{C}-\underset{\underset{CH_2CH_2CH_2CH_3}{|}}{C}HCOOEt + NaBr$$

(b)
$$EtONa + CH_3\underset{\underset{O}{\|}}{C}-\underset{\underset{C_4H_9}{|}}{C}HCOOEt \rightarrow CH_3\underset{\underset{ONa}{|}}{C}=\underset{\underset{C_4H_9}{|}}{C}COOEt + EtOH$$

$$n\text{-}C_4H_9Br + CH_3\underset{\underset{ONa}{|}}{C}=\underset{\underset{C_4H_9}{|}}{C}COOEt \rightarrow CH_3\underset{\underset{O}{\|}}{C}-\underset{\underset{(C_4H_9)_2}{\|}}{C}-COOEt + NaBr$$

(c) $EtONa + H_2C(COOEt)_2 \rightarrow NaHC(COOEt)_2 + EtOH$

$CH_3I + NaHC(COOEt)_2 \rightarrow CH_3HC(COOEt)_2 + NaI$

(d) $EtONa + CH_3HC(COOEt)_2 \rightarrow CH_3(Na)C(COOEt)_2 + EtOH$

$C_4H_9Br + CH_3(Na)C(COOEt)_2 \rightarrow$

$$CH_3(C_4H_9)C(COOEt)_2 + NaBr$$

40.11   Preparation of the Sodium Derivative.   The method of preparation of the sodium derivative is similar for both esters.   The sodium compound usually is prepared with sodium ethoxide since both esters are stronger acids than is alcohol.   The acid dissociation constants are 10^{-9} for acetoacetic ester, and 10^{-20} for alcohol.   Malonic ester is a much stronger acid than alcohol and probably somewhat weaker than acetoacetic ester.

The formation of the sodium salt of the ester is a fairly rapid reaction, since it is essentially the distribution of a metal between two acids, namely, the alcohol and the ester.   Sometimes on cooling and standing the sodio compound separates.   However, the use of sodium ethoxide is not feasible (1) when the reagent next added reacts with alcohol (an acyl halide for example) or (2) if the ester is too weak an acid, as are some monoalkylated malonic esters.   Then the sodio compound may be obtained by the action of sodamide in ammonia solution, or by the action of metallic sodium, usually in the form of sodium wire, or of sodamide on a solution of the reactive ester compound in absolute ether.   The sodium salt often separates as a fine powder.   An objection to the use of metallic sodium is the reduction of some ester (refer to 19.165).   Since liquid ammonia and ether are not satisfactory media for carrying out the reaction of the sodium salt with the halogen compound, because of their low boiling points, a higher-boiling inert liquid such as benzene or toluene is added, and the more volatile liquid is driven off.   This gives a fine suspension of the insoluble sodium salt.

In the preparation of sodium ethoxide, the alcohol should be anhydrous, and the sodium should be clean, that is, free of oxide and hydroxide, since sodium hydroxide saponifies the esters to salts, and these do not form reactive sodium compounds.

$EtOCOCH_2COOEt + NaOH \rightarrow EtOCOCH_2COONa + EtOH$

$CH_3COCH_2COOEt + NaOH \rightarrow CH_3COCH_2COONa + EtOH$
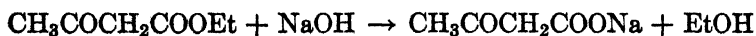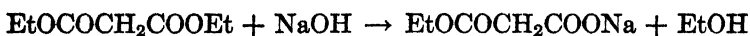
If the amount of sodium is 0.5 g. atom or less, it can be added all at once if in large pieces.   This has the advantage that undue exposure to air is

avoided, and the reaction is less likely to get out of control than if the sodium is added all at once in the form of small pieces. Cooling by a bath or with wet towels usually is sufficient with 0.5 g. atom in large pieces. Often, especially with large amounts, the sodium is added at intervals down the condenser in the form of thin strips, since control is not possible with large amounts, if added all at once. About 500 ml. of absolute ethyl alcohol is a convenient amount with 1 g. atomic weight of sodium, for the reaction proceeds with reasonable rapidity even toward the end. Usually heat must be applied then.

That the alcohol must be anhydrous is emphasized by the fact that 1% (by volume) of water in the alcohol represents about $\frac{1}{4}$ mole of water, which would form about $\frac{1}{4}$ mole of sodium hydroxide. Water in absolute alcohol is best determined by means of the Karl Fischer reagent (Experiment 19–2). As a precaution, metallic sodium should be added to the absolute alcohol, 3 to 5 g. of sodium per 100 ml. of alcohol, and then the alcohol should be distilled through dry apparatus directly into the reaction flask. Alcohol so distilled will still contain a very small amount of water, because there is a distribution of sodium between the two acids, water and alcohol:

$$HOH + C_2H_5ONa \rightleftharpoons NaOH + C_2H_5OH$$
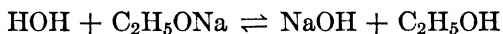
Alcohols other than ethyl can be used. Thus, higher reaction temperatures are possible with higher alcohols, and also these may be made anhydrous, simply by distillation. However, the sodium alkoxide and sodioesters are less soluble in the higher alcohols than in ethyl alcohol.

40.12   The Condensation Reaction. Condensation may be carried out with a variety of compounds, and their reactivities are approximately in the following decreasing order: Acyl halides > allyl halides > benzyl halides > α-halogenated ketones > alkyl sulfates (especially methyl and ethyl) > alkyl p-toluene sulfonates > alkyl halides > alkyl nitrates > halogenated ethers and halogenated alcohols.

Among different alkyl groups, the reactivity is in the order: Methyl > higher primary > secondary > tertiary. The last are introduced with great difficulty, due to slowness of reaction and marked tendency to form unsaturated compounds. Thus, the yields of *tert*-butyl and *tert*-amylmalonic ester in absolute ethyl alcohol at low temperatures are only 6.4 and 4.6%, respectively.

Acyl halides react rapidly, but often form the oxygen esters with acetoacetic ester. Alkyl halides react much more slowly, often requiring heating for several hours for completion of reaction. Although ΔH is negative, there is little danger of the reaction getting out of control,

because of the slow rate, as in Experiment 40–1, The Preparation of n-Butylacetoacetic Ester.

Two groups may be introduced, reactions b and d. Since an ester containing a secondary group is very much less reactive than one containing a primary, the secondary group should be introduced first, if one is to be present. If both groups are identical, they may be introduced in a single operation, even though the reaction takes place in steps.

The completion of the reaction is indicated when the mixture no longer is alkaline, provided the molal ratio of the alkyl halide to sodium is not less than unity.

In Experiment 40–2, The Preparation of Ethyl 1,1-Cyclopropane-dicarboxylate, malonic ester is condensed with ethylene bromide. Both bromine atoms react with the same molecule of the ester to form a cyclopropane ring.

$$EtONa + H_2C(CO_2Et)_2 \rightarrow NaHC(CO_2Et)_2 + EtOH$$

$$BrCH_2CH_2Br + NaHC(CO_2Et)_2 \rightarrow BrCH_2CH_2CH(CO_2Et)_2 + NaBr$$

$$EtONa + BrCH_2CH_2CH(CO_2Et)_2 \rightarrow$$

$$BrCH_2CH_2CNa(CO_2Et)_2 + EtOH$$

$$BrCH_2CH_2CNa(CO_2Et)_2 \rightarrow \begin{array}{c} CH_2 \\ | \\ CH_2 \end{array}\!\!\!\diagup\!\!\!\searrow C(CO_2Et)_2 + NaBr$$
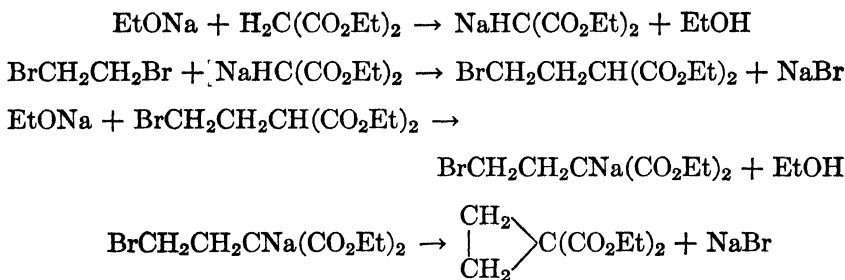
40.13 Coupling. A modification of the condensation reaction is the use of a halogen, for example iodine or bromine or of a suitable dihalogen organic compound: methylene iodide. One molecule of each of these can react with 2 molecules of the sodioester; thus iodine with sodioacetoacetic ester yields diacetylsuccinic ester, as in Experiment 40–3, and methylene iodide with sodiomalonic ester yields α,α'-dicarbethoxyglutaric ester.

$$I_2 + 2CH_3C\!\!=\!\!CHCOOEt \atop \qquad\quad | \atop \qquad\quad ONa \rightarrow \begin{array}{c} O \\ \| \\ CH_3\overset{}{C}CHCOOEt \\ | \\ CH_3\overset{}{C}CHCOOEt \\ \| \\ O \end{array} + 2NaI$$

$$CH_2I_2 + 2NaHC(COOEt)_2 \rightarrow$$

$$(EtOCO)_2CHCH_2CH(COOEt)_2 + 2NaI$$
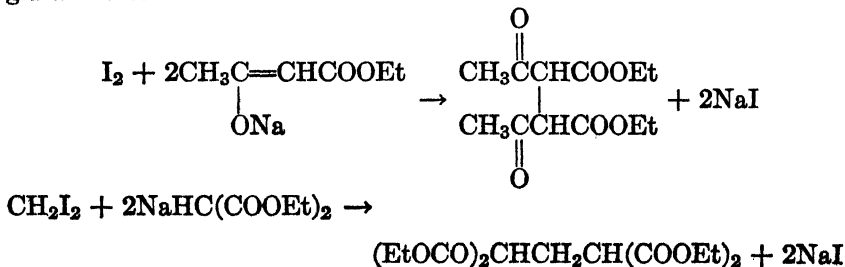
With ethylene bromide, not only coupling but also ring closure may take place, as discussed in 40.12.

40.14 Side Reactions. Unsaturation of the alkyl halide (etc.) is quite extensive with the tertiary compounds and sometimes with secondary ones, but usually is not important with primary compounds. It can be decreased by lowering the temperature. The rate of the condensation reaction is lowered also, however.

Generally, the principal side reactions are those due to the distribution of sodium among the different acids present. In addition to the ester these are alcohol and the monosubstituted ester. With the sodium alkoxide, an alkyl halide yields an ether. With the sodium salt of the monosubstituted ester, an alkyl halide gives a disubstituted ester.

$$C_2H_5OH + NaCH(CO_2Et)_2 \rightleftharpoons CH_2(CO_2Et)_2 + C_2H_5ONa$$

$$HCR(CO_2Et)_2 + NaCH(CO_2Et)_2 \rightleftharpoons$$

$$CH_2(CO_2Et)_2 + NaCR(CO_2Et)_2$$

$$C_2H_5ONa + RX \rightarrow NaX + C_2H_5OR$$

$$NaCR(CO_2Et)_2 + RX \rightarrow NaX + R_2C(CO_2Et)_2$$
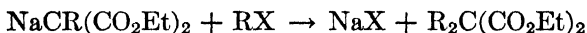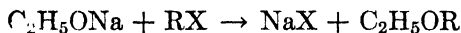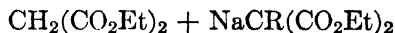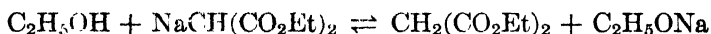
The ether reaction usually is not important, but the reaction of the sodium salt of the substituted ester may be quite extensive. This can be diminished by taking an excess of the ester initially. Thus, in many cases yields on the basis of an alkyl halide can be raised from 50 to 85% and sometimes even to 90%. Yields may be improved by carrying out the reaction with the suspension of the sodium compound in an inert liquid, such as benzene or toluene.

Another side reaction which may take place with acetoacetic ester is the attachment of the entering radical to the oxygen atom instead of to the carbon atom. This is noted when the reagent is especially reactive as with an acyl halide. Thus acetyl chloride forms two products, namely:

$$CH_3C{=}CHCOOEt \qquad \text{and} \qquad CH_3C{-}CH{-}COOEt$$
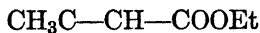
$$\underset{\text{ethyl } \beta\text{-acetoxycrotonate}}{\overset{|}{OCOCH_3}} \qquad\qquad\qquad \underset{\text{ethyl diacetylacetate}}{\overset{\|}{O}\ \ \overset{|}{COCH_3}}$$

The formation of the oxygen derivative takes place also with ethyl chloroformate but usually is not important with alkyl halides. Sometimes, as for example in the case of ethyl chloroformate, coupling to the oxygen atom may be minimized by using the copper derivative of acetoacetic ester. This is prepared by adding a saturated alcoholic solution of cupric acetate to the ester. The copper salt separates as a precipitate.

In the formation of ethyl cyclopropane-1,1-dicarboxylate, the side reactions are somewhat more complicated, since the product of the first condensation still has a reactive halogen atom. The most important side reactions, from the standpoint of malonic ester, are bimolecular-condensation reactions which lead to higher molecular-weight compounds.

(1) $(EtOCO)_2CHNa + BrCH_2CH_2CH(CO_2Et)_2 \rightarrow$

$(EtOCO)_2CHCH_2CH_2CH(CO_2Et)_2 + NaBr$

(2) $(EtOCO)_2CHCH_2CH_2 + BrCH_2CH_2C(CO_2Et)_2 \rightarrow$
$\qquad\qquad\quad |\qquad\qquad\qquad\qquad |$
$\qquad\qquad\quad Br\qquad\qquad\qquad\quad Na$

$(EtOCO)_2CHCH_2CH_2 + NaBr$
$\qquad\qquad\qquad\quad |$
$\qquad\qquad\quad BrCH_2CH_2C(CO_2Et)_2$

(3) $BrCH_2CH_2 + BrCH_2CH_2C(CO_2Et)_2 \rightarrow$
$\quad\;\; |\qquad\qquad\qquad |$
$\quad\;\; Br\qquad\qquad\quad Na$

$BrCH_2CH_2C(CO_2Et)_2$
$\qquad\qquad |\qquad\qquad\qquad + NaBr$
$\quad\; BrCH_2CH_2$
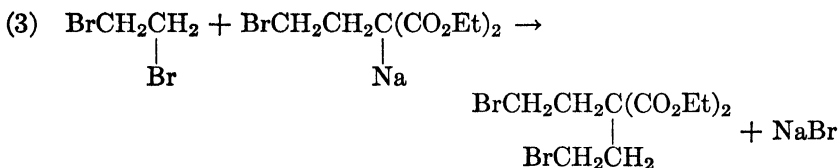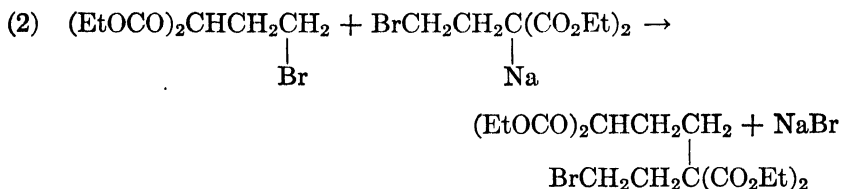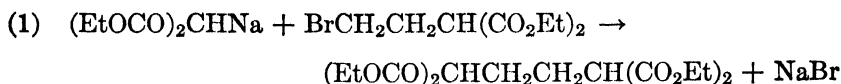
A satisfactory yield of the cyclopropane compound depends on holding reactions 1, 2, and 3 to a minimum. In Experiment 40–2, reaction 1 is minimized during the first coupling by having a large excess of ethylene bromide initially and running sodiomalonic ester into it, for then the sodiomalonic ester reacts largely with ethylene bromide, rather than with the γ-bromoester. Reactions 2 and 3 are possible, during the primary coupling, because of the redistribution of sodium (4).

(4) $(EtOCO)_2CHNa + BrCH_2CH_2CH(CO_2Et)_2 \rightleftharpoons$

$(EtOCO)_2CH_2 + BrCH_2CH_2CNa(CO_2Et)_2$
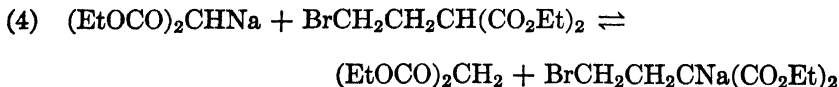
Reaction 4 probably is much faster than the primary coupling reaction. The undesirable effects here, which arise from subsequent reactions 2 and 3, are minimized by dilution. These last reactions become more important with the addition of the second mole of sodium ethoxide. Reaction 3 can be largely eliminated by removal of the excess ethylene bromide by distillation before the second mole of sodium ethoxide is added. If it is distilled off, the volume must be restored by addition of more solvent before the second mole of sodium ethoxide is added so as to maintain dilution and diminish reaction 2. However, since the yield

of 70% is regarded as satisfactory when the excess bromide is not removed, the extra labor involved in its removal does not seem warranted in small-scale experiments. The yield is only 25 to 30% when ethylene bromide is added slowly to an equal molal quantity of sodium malonic ester in alcohol in the conventional manner for malonic ester syntheses.

40.15 Recovery. Usually most of the alcohol is removed by distillation, either by heating on a steam bath until alcohol no longer distils, or preferably by heating in an oil bath to 125–135° with mechanical stirring. Then the reaction mixture is poured into water to dissolve inorganic salts and residual alcohol. If most of the alcohol has not been removed first, the separation of the ester is incomplete, since alcohol acts as a mutual solvent for the ester and for water. In case the two phases separate well at this point, the simplest procedure involves washing the organic phase a few times with cold water and then at once subjecting it to vacuum distillation, thus removing water at a relatively low temperature. This minimizes hydrolysis, which takes place slowly even at room temperature.

$$\text{EtOCOCH}_2\text{COOEt} + \text{HOH} \rightarrow \text{EtOCOCH}_2\text{COOH} + \text{EtOH}$$

$$\text{CH}_3\text{COCH}_2\text{COOEt} + \text{HOH} \rightarrow \text{CH}_3\text{COCH}_2\text{COOH} + \text{EtOH}$$
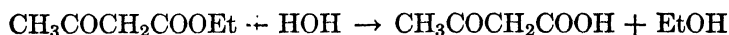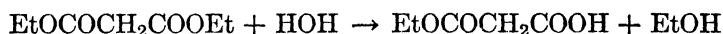
In case the two phases do not separate well, partly because of similarity in density, ethyl ether or some other suitable volatile solvent can be added (refer to Subsection 6.16, Emulsions). If the amount added is not too large, the afore-mentioned procedure can be followed.

In case the distillation cannot be carried out immediately following the washing operation, water must be removed from the ester. This is most rapidly accomplished by reducing the viscosity of the ester with ether, adding a suitable drying agent, and stirring mechanically. The ether is removed by distillation at atmospheric pressure.

40.16 Compounds Reacting like Malonic Ester and Acetoacetic Ester. The reactions of malonic ester are shown by other compounds which have a reactive methylene group, that is, —CH$_2$—, to which are attached two radicals which activate this group. The approximate order of activating influence of different radicals, in decreasing effect is: nitro, —NO$_2$ > cyano, —CN > formyl, —CHO > acyl, —COR > carbalkoxy, —COOR > carbamido, —CONH$_2$. The two radicals need not be alike. Thus other typical reactive compounds are ethyl cyanoacetate N≡C—CH$_2$COOC$_2$H$_5$ and acetylacetone CH$_3$COCH$_2$COCH$_3$, from which both mono- and disubstituted derivatives can be prepared. The relative reactivity of cyanoacetic and malonic ester is illustrated by the observation that two isopropyl groups can be

introduced easily into cyanoacetic ester, but with difficulty into malonic ester. In general other α-acyl esters, for example ethyl α-propionyl propionate, form reactive sodium compounds.

40.17 Hydrolysis of Malonic Esters. A substituted malonic ester can be hydrolyzed to the salt of the substituted malonic acid by heating with dilute alkali. The free acid may then be isolated by acidification in the cold. The free malonic acid decarboxylates easily, and, if the solution of the sodium salt is acidified with excess hydrochloric acid and boiled, the malonic acid is converted to the substituted acetic acid:

$$(e) \qquad \begin{matrix} CH_3 \\ \diagdown \\ \diagup \\ C_4H_9 \end{matrix} C(COOH)_2 \rightarrow CH_3(C_4H_9)CHCOOH + CO_2$$
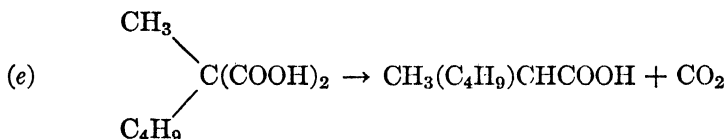
40.18 Hydrolysis of Acetoacetic Esters. A substituted acetoacetic ester may be hydrolyzed to yield (f) and (g) the keto acid, (h) and (i) a ketone, or (j) an acid:

(f) $\quad$ NaOH + $CH_3COCH(C_4H_9)COOEt \longrightarrow$

$$CH_3COCH(C_4H_9)COONa + EtOH$$

$\quad$ $H_2SO_4 + CH_3COCH(C_4H_9)COONa \longrightarrow$

$$CH_3COCH(C_4H_9)COOH + NaHSO_4$$

(g) $\quad$ HOH + $CH_3COCH(C_4H_9)COOEt \longrightarrow$

$$CH_3COCH(C_4H_9)COOH + EtOH$$

(h) $\quad$ $CH_3COCH(C_4H_9)COOH \longrightarrow CH_3COCH_2C_4H_9 + CO_2$

(i) $\quad$ $H_2O + CH_3COCH(C_4H_9)COOEt \xrightarrow{H_2SO_4}$

$$CH_3COCH_2C_4H_9 + CO_2 + EtOH$$

(j) $\quad$ 2KOH + $CH_3COCH(C_4H_9)COOEt \longrightarrow$

$$CH_3COOK + C_4H_9CH_2COOK + EtOH$$
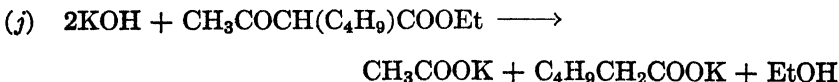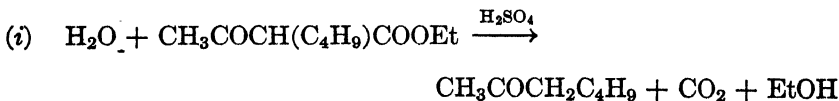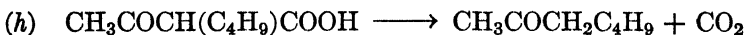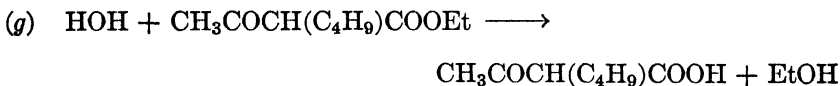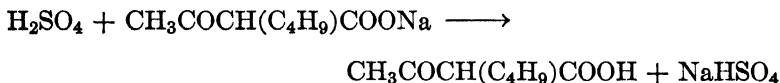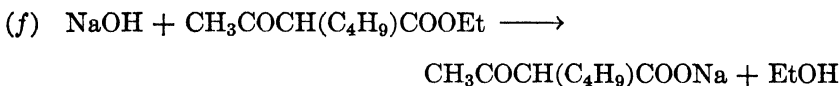
Since the free acids are not very stable, they can be obtained only under carefully controlled conditions, as for example saponification with dilute sodium hydroxide at room temperature for several hours (usually one day), followed by acidification and extraction with ether (f), or merely by slow hydrolysis with water alone (g). The formation of the ketone takes place when the free acid is heated (h) (in some cases the

acid decomposes spontaneously) or when the ester is boiled with dilute alkali (aqueous or alcoholic), barium hydroxide solution or dilute sulfuric acid (*i*) (the ketonic scission). On the other hand the acidic scission (*j*) takes place when the ester is boiled with concentrated potassium hydroxide solution, either aqueous or alcoholic. Even under optimum conditions for one type of decomposition, some of the other reaction takes place.

Experiment 40–1   General Method of Preparing Substituted Acetoacetic Esters

Ethyl *n*-Butylacetoacetate (*n*-Butylacetoacetic Ester)

Equip a dry 1-liter three-necked flask with a dry reflux condenser (Note 1), a dropping (or separatory) funnel, and a sealed mechanical stirrer (Note 2). Support the flask so that it can be heated by an oil bath later. Protect the condenser and dropping funnel with suitable drying tubes.

Prepare 0.50 mole of sodium ethoxide by adding, to 250 ml. of absolute ethyl alcohol (Note 3) in the flask, 0.50 g. atomic weight of clean metallic sodium (Notes 4 and 5) in as few pieces as possible (Note 6). If the alcohol is anhydrous and the sodium metal is in a few large pieces, the reaction should not get out of control. Should the boiling be too vigorous, cool somewhat with a water bath, or by means of a wet towel (Note 7). Towards the last, when the reaction slackens, it should be necessary to apply heat.

Bring the temperature to boiling, and, while stirring gently, add 0.50 mole of recently distilled ethyl acetoacetate (Note 8) fairly rapidly. Then, without needless delay allow to run in, as rapidly as consistent with good control, an amount of *n*-butyl bromide (Notes 9 and 10) 10 to 15% excess over the amount of sodium. Keep the liquid boiling. As solid separates, increase the rate of stirring, and use an oil or wax bath as source of heat, to minimize bumping (Note 11). Continue the heating until a drop of the solution, when added to moist litmus paper, shows a neutral reaction (Note 12).

By means of a short wide tube attach a condenser for downward distillation, and remove alcohol rapidly by raising the bath temperature to 100°, and finally to 130° or 140°, while stirring vigorously (Note 13).

Set up an apparatus for vacuum distillation, preferably the simpler setup of Figure 8–5. The Claisen distilling flask should have a 5- to 10-cm. column of glass rings in the neck. Have ready three similar-sized

receiver flasks for making cuts. Obtain approval of the instructor. The apparatus must be air-tight, and the air-leak tube should admit only the minimum of air (refer to Chapter 8).

After the vacuum-distilling apparatus is ready, add to the cold reaction mixture enough pure cold water (or water and ice), 0.2 to 0.5 liter to dissolve the solid. Agitate with a whirling motion (Note 14). Keep cold. Carry out the subsequent operations without needless delay. Separate the phases (Note 15), remove residual salts and alcohol by carefully washing the organic phase a few times with pure cold water, then transfer it to the distilling flask, reduce the pressure to about 20 mm., and remove water by distillation as rapidly as feasible until the distilling temperature is about 55°, by raising the bath temperature to about 90°.

Change the receiver, and distil *slowly*, gradually increasing the bath temperature until the distilling temperature becomes fairly constant at about 110° or 120°, changing receivers at about 85° if much unreacted ethyl acetoacetate distils. Again change the receiver, and collect the ethyl *n*-butylacetoacetate in a range of about 5° near the boiling point (Note 16). In case the separation between unchanged ethyl acetoacetate and ethyl *n*-butylacetoacetate was not good, as shown by the fact that considerable material distilled between 85° and the temperature where the last cut was made, this fraction should be redistilled at reduced pressure. Calculate the percentage yield of product (Note 17).

Notes

1. It is essential that no water be present, due either to wet apparatus or more especially to leakage from the condenser. Thus, a water or steam bath should be avoided, and connections should be made with rubber stoppers.

2. The stirrer is especially useful during the removal of alcohol later by distillation.

3. Absolute alcohol slowly absorbs water from the atmosphere if kept in ordinary containers. The water content should be 0.5% or lower (refer to 40.11).

4. It is desirable that the reaction between moisture of the air and the sodium be minimum. Therefore, the sodium should be free of crust and should have a minimum of surface.

5. *Caution:* Use tongs or paper for handling, and always set the sodium on paper. Do not allow metallic sodium to come in contact with the wooden desk tops, which are destroyed by it. *Do not throw pieces of metallic sodium, even scraps, into the sinks,* but put them in alcohol. After the reaction in alcohol has slackened, add water in small portions. When the sodium has dissolved *completely*, pour the liquid down the sink.

6. The sodium can be put in through the large center neck by removing the mechanical stirrer, which is not needed until later.

7. The reaction should proceed rapidly but not so vigorously that more than slight cooling is necessary. The worker should take warning from any overvigorous reaction that too much water may be present.

8. Or ethyl malonate, if a substituted malonic ester is to be prepared. Potassium iodide is believed to increase the rate of reaction. The effect of adding 5 to 10 g. should be investigated.

9. Or other alkyl halide, if some other substituted ethyl acetoacetate is to be prepared.

10. In case two unlike radicals are to be introduced, as in the preparation of ethyl ethyl-n-butylacetoacetate, prepare a second 0.50 mole of sodium ethoxide while the reaction is proceeding, and add it to the reaction mixture as soon as the reaction is finished, following at once with 0.50 mole of the second alkyl halide.

In case two like radicals are to be introduced, as in the preparation of ethyl di-n-butylacetoacetate, twice the amount of n-butyl bromide may be added to ethyl acetoacetate at the start, and then twice the amount of sodium ethoxide may be added to the boiling solution as rapidly as consistent with control of temperature, heating until reaction is over. However, the yield is low.

11. Check for unsaturation by attaching a tube to the condenser outlet, to see if any olefin is being evolved. This is especially important if the reactant is a tertiary or secondary alkyl halide.

In case unsaturation is observed, the temperature must be lowered and the reactant added more slowly.

If there is no complication from unsaturation, the alkyl halide may be added as rapidly as control of temperature permits, cooling by a water bath or by wet towels if necessary. Do not reduce the temperature much below boiling, for then the rate is decreased.

12. Usually about 2 hours' heating is necessary.

13. Rapid distillation is especially desirable when an excess of a halogen compound has been added, so as to distil as much of it as possible with the alcohol. Dilution of the distillate with water or, better, with an aqueous salt solution throws out the halide. The excess halogen compound should be recovered and purified. The yield should be calculated from the amount consumed.

14. In case the tap water is "hard," distilled water is preferred so as to avoid the troublesome emulsion resulting from insoluble salts. About 75 ml. of water is sufficient for dissolving the sodium bromide, but more is necessary in order to extract alcohol more completely. Vigorous shaking is more likely to cause emulsion formation than mixing by swirling. However, continue until good extraction is assured.

15. In case the phases do not separate well or an emulsion develops, refer to the discussion and to Subsection 6.16, Emulsions. Sometimes removal of insoluble material by filtering the mixture with suction allows the two phases to separate better. Often emulsification is promoted by not adding sufficient water. Sometimes it is necessary to add ether or other suitable volatile solvent. The solvent can be removed at reduced pressure without drying, if the distillation is done without delay.

In case the distillation cannot be performed at once, add ether anyway, about 200 ml., to reduce the viscosity. After thorough washing with water, dry as completely as possible with a suitable drying agent before setting aside (refer to Chapter 12). Remove the drying agent completely. Recover the ether by distillation at atmospheric pressure until the bath temperature is about 60°, and then *let cool* before reducing the pressure.

16. Distilling temperatures are: ethyl acetoacetate, 180° at 755 mm., 80° at 18 mm.; ethyl n-butylacetoacetate, 115–117° at 16 mm.; ethyl malonate, 93–94° at 20 mm.; ethyl n-butylmalonate, 140–145° at 40 mm., 130–135° at 20 mm. For values at other pressures, refer to Figure 8–2. If difficulty is experienced in distilling over the desired product, transfer it to a flask with less unheated surface.

17. Yield is 60 to 70%.

Questions

1. Show by equations why water is detrimental.
2. Could the other three butyl bromides be used in place of n-butyl bromide with expectation of as good a yield?
3. What factors favor the formation of butyl ethyl ether?
4. How does the addition of sodium ethoxide in small portions, rather than all at once, affect ether formation in the preparation of a symmetrical dialkyl derivative, following the procedure of Note 10?
5. What is the disadvantage of not removing the crust on the pieces of metallic sodium?
6. Why is it desirable to take an excess of the alkyl halide?
7. Why is it desirable to remove most of the alcohol before adding water to the reaction mixture?
8. Why should the reaction mixture, after removal of alcohol, be cooled before water is added?
9. Explain why filtering sometimes aids in breaking emulsions.
10. Explain why the addition of ether often facilitates separation of the phases.
11. Why is it unwise to try to dry the crude reaction product with a solid drying agent?
12. Why not drive out the water by distilling at atmospheric pressure?
13. How do you account for the presence of unreacted ethyl acetoacetate?
14. Explain why, in terms of other compounds easily obtainable from your product, ethyl acetoacetate is useful for synthesis.
15. Compare acetoacetic and malonic esters in regard to their value in synthesis.
16. What are the main impurities in the crude and final products?
17. What steps have been taken to remove them?

Experiment 40–2   Preparation of Ethyl
Cyclopropane-1,1-dicarboxylate

Equip a dry 1-liter three-necked flask with a dry reflux condenser (Note 1), a dropping (or separatory) funnel, and a sealed mechanical stirrer (Note 2). Support the flask so it can be heated by an oil bath later. Protect the condenser and dropping funnel with suitable drying tubes. Place 1 mole of ethylene bromide in the flask.

In a second dry flask (0.5 or 1.0 liter) equipped with a reflux condenser and a drying tube, prepare 0.50 mole of sodium ethoxide by adding to 250 ml. of absolute ethyl alcohol (Note 3) in the flask, 0.50 g. atomic weight of clean metallic sodium (Notes 4 and 5) in as few pieces as possible (Note 6). If the alcohol is anhydrous and the sodium metal is

in a few large pieces, the reaction should not get out of control. Should the boiling be too vigorous, cool somewhat with a water bath or by means of a wet towel (Note 7). Toward the last, when the reaction slackens, it should be necessary to apply heat.

When all the sodium has dissolved, cool the mixture to *ca.* 35°, and add 0.50 mole of ethyl malonate (malonic ester, Notes 8 and 9). Pour the mixture into the dropping funnel, and add it gradually with stirring to the ethylene bromide over a period of 1.5 hours, keeping the bath at 75° to 80°. In case unsaturation takes place with the formation of vinyl bromide, lower the temperature somewhat (Note 10).

During this addition, prepare another 0.5 mole of sodium ethoxide in 250 ml. of absolute alcohol as before (*Caution:* Notes 4 and 5). As soon as the sodium malonic ester has been run in, add the second 0.5 mole of sodium ethoxide through the dropping funnel as rapidly as feasible. At this point the mixture may either be refluxed for 2 hours or allowed to stand overnight (Note 11).

Raise the bath temperature above 100°, (110° to 125°), and, while stirring rapidly, distil with a minimum of fractionation the greater part of the solvent through a short wide exit tube into a condenser arranged for downward distillation (Note 12). Let the contents cool to 15° or 20°. Recover the excess ethylene bromide in the distillate by diluting it with two or three volumes of water, separating, washing three or four times with water, and drying with calcium chloride. Weigh in order to calculate the amount used in the reaction, and place in the bottle of ethylene bromide residues.

Set up an apparatus for vacuum distillation, preferably the simpler setup of Figure 8–5. The Claisen distilling flask should have a 5- to 10-cm. column of glass rings in the neck. Have ready three similar-sized receiver flasks for making cuts. Obtain approval of the instructor. The apparatus must be air-tight, and the air-leak tube should admit only the minimum of air (refer to Chapter 8).

After the vacuum-distilling apparatus is ready, add to the cold reaction mixture enough pure cold water (or water and ice), 0.2 to 0.5 liter, to dissolve the solid (Note 13). Agitate with a swirling motion. Keep cold. Carry out the subsequent operations without needless delay. Separate the phases (Note 14), remove residual salts and alcohol by carefully washing the organic phase a few times with pure cold water, and then transfer it to the distilling flask; reduce the pressure to about 20 mm., and remove water by distillation as rapidly as feasible until the distilling temperature is about 55°, by raising the bath temperature to about 90°.

Change the receiver, and distil *slowly*, gradually increasing the bath temperature until the distilling temperature becomes fairly constant at about 100°, changing receivers at about 100° if much unreacted ethyl malonate has distilled. Again change the receiver, and collect the ethyl cyclopropane-1,1-dicarboxylate in a range of about 5° near the boiling point (Note 15). In case the separation between unchanged ethyl malonate and ethyl cyclopropanedicarboxylate was not good, as shown by the fact that considerable material distilled between 95° and the temperature where the last cut was made, this fraction should be redistilled at reduced pressure. Calculate the percentage yield of product.

Notes

1. It is essential that no water be present, due either to wet apparatus or more especially to leakage from the condenser. Thus, a water or steam bath should be avoided, and connections should be made with rubber stoppers.

2. The stirrer is especially useful during the removal of alcohol later by distillation.

3. Absolute alcohol slowly absorbs water from the atmosphere if kept in ordinary containers. The water content should be 0.5% or lower (refer to 40.11).

4. It is desirable that the reaction between moisture of the air and the sodium be a minimum. Therefore, the sodium should be free of crust and should have a minimum of surface.

5. *Caution:* Use tongs or paper for handling, and always set the sodium on paper. Do not allow metallic sodium to come in contact with the wooden desk tops, which are destroyed by it. *Do not throw pieces of metallic sodium, even scraps, into the sinks,* but put them in alcohol. After the reaction in alcohol has slackened, add water in small portions. When the sodium has dissolved *completely,* pour the liquid down the sink.

6. The sodium can be put in through the large center neck by removing the mechanical stirrer, which is not needed until later.

7. If the water content of the alcohol is satisfactory and the sodium is cut into only three or four pieces, the reaction should proceed rapidly but not so vigorously that more than slight cooling is necessary. The worker should take warning from any overvigorous reaction that the alcohol contains water.

8. It is essential that the ester be recently distilled, since it slowly absorbs moisture on standing and undergoes hydrolysis.

9. Some of the sodium salt of malonic ester may precipitate from this solution. This is especially troublesome if it happens in the dropping funnel. Therefore, keep most of the solution in the flask in which it is easy to redissolve any solid by warming or by the addition of more absolute alcohol (20 to 50 ml.).

10. To test for vinyl bromide attach a tube by an air-tight connection to the condenser outlet, and pass any gas through water or other suitable liquid, taking care that the liquid is not drawn into the apparatus.

11. The reaction mixture should become practically neutral.

12. The alcohol and much of the excess ethylene bromide distil over below 100° if there is little or no fractionation. Distillation is greatly aided by agitation.

13. In case the tap water is "hard," distilled water is preferred so as to avoid the troublesome emulsion resulting from insoluble salts. About 150 ml. of water is sufficient for dissolving the sodium bromide, but more is necessary in order to extract alcohol more completely. Vigorous shaking is more likely to cause emulsion formation than mixing by whirling. However, continue until good extraction is assured.

14. In case the phases do not separate well, or an emulsion develops, refer to the discussion and to Subsection 6.16, Emulsions. Sometimes removal of insoluble material by filtering the mixture with suction allows the two phases to separate better. Often emulsification is promoted by not adding sufficient water. Sometimes it is necessary to add ether or other suitable volatile solvent. The solvent can be removed at reduced pressure without drying if the distillation is done without needless delay.

In case the distillation cannot be performed at once, add ether anyway, about 200 ml., to reduce the viscosity. After thorough washing with water, dry as completely as possible with a suitable drying agent before setting aside (refer to Chapter 12). Remove the drying agent completely. Recover the ether by distillation at atmospheric pressure until the bath temperature is about 60°; then *let cool* before reducing the pressure.

15. The boiling points at 20 mm. are: malonic ester 93° to 94°, ethyl cyclopropane-1,1-dicarboxylate 104° to 107°. Yield, 75 to 80%. Yields have been as high as 89%, when the reaction mixture stood for a week. When ethylene bromide is replaced by trimethylene bromide, the yield of the corresponding cyclobutane compound (b.p., 110–112° at 18 mm.) is 50%. More polymer is formed in this case. If difficulty is experienced in distilling over the product, transfer it to a flask having less unheated surface.

Questions

1. Why must water be excluded in this preparation?

2. Suppose ethylene bromide were added slowly to the sodium malonic ester. Would you expect a different result? Explain.

3. Suppose it were added as rapidly as possible, consistent with good control of the temperature. Would you expect the result to be as good or better, compared to the procedure of Question 2?

4. If the recovered ethylene bromide is taken into account, is the yield as satisfactory as on the ester basis? If not, how do you account for the difference?

5. Why should the concentrated reaction mixture be cooled before water is added?

6. Why filter even when enough water is present to dissolve the sodium bromide?

7. Explain why removal of excess ethylene bromide, if done before the second portion of sodium ethoxide is added, might lead to an increased yield.

8. Explain why the addition of ether often facilitates separation of the phases.

9. Why is it unwise to try to dry the crude reaction product with a solid drying agent?

10. Why not drive out the water by distilling at atmospheric pressure?

11. Why is loss insignificant when a 500-ml. distilling flask is used?

12. What reactions would you suggest as a means of obtaining cyclopropane monocarboxylic acid and cyclopropane from the ester you prepared?

13. By what other reactions may cyclopropane be prepared?

14. What is the advantage of increasing the amount of sodium ethoxide?

15. Why not add all the sodium compound at once to the ethylene bromide, assuming that the reaction mixture would not get out of control?

16. What is the structure of vinylmalonic ester? How could it be a reaction product?

17. What is formed by the action of water on ethyl malonate?

18. Compare malonic and acetoacetic esters in regard to their value in synthesis.

19. What are the main impurities in the crude and final products?

20. What steps have been taken to remove them?

Experiment 40–3   Preparation of Diethyl Diacetylsuccinate

Equip a dry flask with a dry reflux condenser, mercury-sealed stirrer, and separatory funnel, and protect all outlets to the air against water vapor. Place 400 to 500 ml. of anhydrous ether (Note 1) in the flask and then 0.3 mole of fine sodium wire (Note 2). Cool, and add slightly less than the theoretical amount (Note 3) of ethyl acetoacetate (recently distilled at reduced pressure) in portions during the course of 10 to 20 minutes, or as rapidly as the reaction can be kept under control (Note 4). Allow the mixture to stand until all of the sodium has reacted, usually 1 or 2 days (Note 5).

Add with stirring a solution of dry iodine in absolute ether containing about 90% of the theoretical amount (Notes 1 and 6). Continue until the iodine color persists for about 1 minute after addition. The reaction is quite rapid. Filter through a dry fluted filter into a dry distilling flask with minimum evaporation and exposure to moisture of the air (*Caution:* no flames near). Extract the solid with more ether, filter as before, and combine the extracts, which should be clear and free of any solid (Note 7). Distil the ether, taking the usual precautions (Note 8) and heating on a warm water bath until the volume is reduced to one third or one fourth, but not until the residual liquid is viscous.

Pour the residue while still warm into a small beaker (later covered) or flask. Prevent rapid evaporation of the ether, and let the diethyl diacetylsuccinate crystallize on standing (Note 9). If the mass should become so solid that suction filtration is not practical, remove any liquid by absorption, using porous tile or good absorbing paper.

Recrystallize from aqueous methanol, aqueous ethanol, or ligroin (60–80°). Determine melting point and percentage yield (Note 10).

Notes

1. Do not assume that the ether is anhydrous merely because it is so labeled. Add some metallic sodium (shavings or wire) in order to make sure. It is important that no water be present; otherwise, sodium hydroxide would be formed. Therefore, take special precautions to keep the reaction mixture anhydrous throughout the experiment. Connections must be tight.

2. For the preparation of sodium wire use a sodium press. It is best to weigh the amount of sodium actually in the flask. *Caution:* See Experiment 40–1, Note 5.

3. Any unchanged ethyl acetoacetate hinders crystallization of the product. Take about 95% of the theoretical amount, or use a 5% excess of metallic sodium.

4. Mix with an occasional whirling motion, but do not use the stirrer, for stirring badly tangles the sodium wire. After standing 1 day it usually is safe to stir.

5. The sodium is converted into a voluminous white solid which may retain the form of the sodium wire. Aside from the fact that some darkening takes place, there is no great harm done in letting the reaction mixture stand longer than 2 days. Darkening is due to oxidation by air. However, rubber stoppers swell badly when left long in contact with ether vapor.

6. The iodine will dissolve more rapidly if pulverized. More may be added, but an excess should be avoided since it discolors the product. Note that the removal of sodium iodide, by filtration, later, is more difficult, the more finely divided it is.

7. Add alcohol to the solid residue to react with any metallic sodium before adding water.

8. *Caution:* Refer to Experiment 14–3. If a flame is used, the residual liquid is liable to be overheated. Pour the ether down the hood sink with a good stream of water.

9. If a gum forms, stir in a small amount of solvent (ether or alcohol) to decrease the viscosity. The mixture may be allowed to stand overnight. However, exposure to air results in darkening.

10. The pure compound melts at 88°; yield, 50%. It can be used in Experiment 44–1, Preparation of α,α'-Dimethylpyrrole.

Questions

1. Why is the presence of sodium hydroxide objectionable?

2. What is the effect of alcohol in the ether?

3. What is the reaction of iodine with the sodium salt of acetoacetic ester?

4. How does the initial rate compare with the rate after three fourths of the sodio-acetoacetic ester has reacted?

5. How does the presence of ethyl acetoacetate hinder crystallization of the product?

6. How do you account for the fact that usually the calculated amount of iodine is too much?

7. What is the objection to adding a good excess of iodine?

8. What is formed by the action of the following on sodioacetoacetic ester: methyl iodide, acetic acid, ethyl chloroacetate, acetyl chloride, bromobenzene, bromine (1 mole)?

9. What is the main impurity in the crude and final product?

10. State the steps taken to remove it.

HYDROXY ACIDS

The general methods of preparation of hydroxy acids are (*a*) the hydrolysis of halogenated acids, (*b*) the hydrolysis of cyanohydrins, (*c*) the reaction of *alpha*-halogenated fatty-acid esters with aldehydes or ketones in the presence of zinc (Reformatsky reaction), (*d*) the oxidation of glycols, (*e*) the reduction of ketoesters, (*f*) the hydration of unsaturated acids, (*g*) the action of nitrous acid on amino acids.

(*a*) $CH_3CHBrCOONa + H_2O \longrightarrow CH_3CHOHCOOH + NaBr$

(*b*) $CH_3CHO + HCN \underset{\longleftarrow}{\overset{CN^-}{\longrightarrow}} CH_3CHOHCN$

$CH_3CHOHCN + HCl + 2H_2O \longrightarrow$

$$CH_3CHOHCOOH + NH_4Cl$$

$HOCH_2CH_2Cl + KCN \longrightarrow HOCH_2CH_2CN + KCl$

$HOCH_2CH_2CN + HCl + 2H_2O \longrightarrow$

$$HOCH_2CH_2COOH + NH_4Cl$$

(*c*) $(CH_3)_2CO + BrCH_2COOC_2H_5 + Zn \longrightarrow$

$$(CH_3)_2C\overset{\diagup OZnBr}{\underset{\diagdown CH_2COOC_2H_5}{}}$$

$$2(CH_3)_2C\overset{\diagup OZnBr}{\underset{\diagdown CH_2COOC_2H_5}{}} + H_2SO_4 \longrightarrow$$

$$2(CH_3)_2C\overset{\diagup OH}{\underset{\diagdown CH_2COOC_2H_5}{}} + ZnBr_2 + ZnSO_4$$

$$(CH_3)_2\overset{\overset{OH}{|}}{C}CH_2COOC_2H_5 + NaOH \longrightarrow$$

$$(CH_3)_2\overset{\overset{OH}{|}}{C}CH_2COONa + C_2H_5OH$$

(d) $CH_3CHOHCH_2OH + O_2 \xrightarrow{Pt} CH_3CHOHCOOH + H_2O$

(e) $CH_3\overset{\displaystyle O}{\overset{\|}{C}}\!-\!CH_2COOC_2H_5 + 2Na + 2C_2H_5OH \longrightarrow$

$$CH_3CHOHCH_2COOC_2H_5 + 2C_2H_5ONa$$

$CH_3CHOHCH_2COOC_2H_5 + NaOH \longrightarrow$

$$CH_3CHOHCH_2COONa + C_2H_5OH$$

(f) $CH_3CH{=}CHCOOH + H_2O \overset{H_3O^+}{\underset{\longleftarrow}{\longrightarrow}} CH_3CHOHCH_2COOH$

(g) $CH_3CHNH_2COOH + HNO_2 \longrightarrow$

$$CH_3CHOHCOOH + N_2 + H_2O$$

41.11   Replacement of Halogen Atoms by the Hydroxyl Group.
Method a is more important for the preparation of α and γ than for
β-hydroxy acids.   In general, salts of acids react more rapidly with
water than do the acids themselves; that is, the halogen atom is acti-
vated by the negative charge on the carboxyl oxygen atoms.   Thus
chloroacetic acid may be converted to glycollic acid with water in an
autoclave at a temperature above 100°, or merely by boiling an aqueous
solution with solid calcium (or barium) carbonate.   In the latter case
the reaction products are calcium chloride and calcium glycollate.   Also
γ-bromovaleric acid when boiled with water is hydrolyzed to the corre-
sponding hydroxy acid, which, however, is converted largely to lactone,
even in the presence of water:

$$CH_3\underset{\underset{Br}{|}}{C}HCH_2CH_2C{=}O \rightarrow CH_3\underset{\underset{OH}{|}}{C}HCH_2CH_2C{=}O + HBr$$
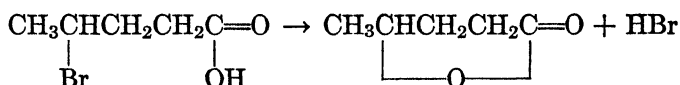
In some cases the hydrolysis rate of the α-halogenated negative ion is
raised by increasing the concentration of the hydroxyl ion; in other cases
there is no effect.   This method is of value in the preparation of many
α-hydroxy acids since α-bromoacids may be prepared by direct bromina-
tion of the corresponding monocarboxylic acid, or by decarboxylation
of the corresponding bromomalonic acid.

This method is usually not satisfactory for the preparation of β-
hydroxy acids, for β-halogenated acids undergo dehydrohalogenation to
the unsaturated acid, even when heated with water, and both dehydro-
halogenation and decarboxylation to olefins, when heated with aqueous
bases.   However, since the unsaturated acid and the hydroxy acid come
to equilibrium (method f) it still is possible to isolate some hydroxy
acid from the hydrolysis mixture.

41.12　The Cyanohydrin Synthesis.　In method *b* an aldehyde or ketone reacts with hydrogen cyanide to form the corresponding cyanohydrin, which undergoes acid hydrolysis to the desired α-hydroxy acid. This is one of the most useful methods for preparing α-hydroxy acids.

The reaction may be carried out with liquid hydrogen cyanide or with a metallic cyanide (sodium or potassium) and some reagent which will furnish hydrogen ions.　This may be a strong acid, as for example nitric acid, as in the preparation of α-hydroxy-α-methylbutyric acid (Experiment 41–1) or one as weak as sodium bisulfite.　Usually a solvent is added, as for example water, alcohol, or sometimes aqueous alcohol, depending on the nature of the reactants.　Water is preferred, especially if a metallic cyanide is used, on account of rapid reaction.

The rate of reaction of hydrogen cyanide with an aldehyde or ketone is quite slow and is markedly accelerated by cyanide ion.　If the reaction is being carried out with liquid hydrogen cyanide, cyanide ion may be introduced by adding a little sodium or potassium cyanide, or some basic substance, for example sodium hydroxide, trimethylamine, pyridine, or other tertiary amine.　An amine is superior in that the system remains homogeneous after it has been added.　(Of course, a primary or secondary amine cannot be used, because of reaction with the oxo compound.)　If a metallic cyanide and an acid are used, there should be at all times an excess of the metallic cyanide.

Actually the reaction is one of cyanide ion, rather than of hydrogen cyanide.　The first reaction product is an ion, which is in equilibrium with the reactants.

$$R_2C{=}O + CN^- \;\rightleftharpoons\; R_2C{-}O^-$$
$$\underset{\textstyle CN}{\vert}$$
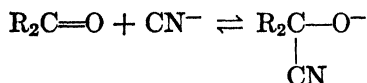
The equilibrium in this reaction lies far on the side of cyanide ion. Subsequently the cyanohydrin ion takes on a proton, thus forming the cyanohydrin.

$$R_2C{-}O^- + HCN \;\rightleftharpoons\; R_2C{-}OH + CN^-$$
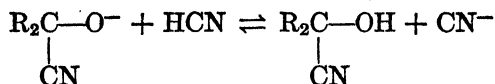
The equilibrium in this reaction lies well to the right.

In the over-all reaction of hydrogen cyanide with an aldehyde or ketone, usually the equilibrium lies well on the side of the cyanohydrin. The equilibrium constants,

$$K = \text{(cyanohydrin)/(oxo compound)(HCN)}$$

for a variety of aldehydes and ketones are shown in Table 41–1.

TABLE 41-1

CYANOHYDRIN EQUILIBRIUM CONSTANTS IN 96% ALCOHOL AT 20°

CHO—C$_6$H$_5$	213	Cyclopentanone	67
o-CHO—C$_6$H$_4$—NO$_2$	1430	Cyclohexanone	380
m-CHO—C$_6$H$_4$—NO$_2$	370	CH$_3$COCH$_3$	32.8
p-CHO—C$_6$H$_4$—NO$_2$	55	CH$_3$COC$_2$H$_5$	37.8
o-CHO—C$_6$H$_4$—Cl	1000	CH$_3$COC$_3$H$_7$-n	28.2
m-CHO—C$_6$H$_4$—Cl	400	CH$_3$COC$_3$H$_7$-i	64.5
p-CHO—C$_6$H$_4$—Cl	204	CH$_3$COC$_4$H$_9$-n	31.3
o-CHO—C$_6$H$_4$—OCH$_3$	385	CH$_3$COC$_4$H$_9$-t	32.3
m-CHO—C$_6$H$_4$—OCH$_3$	233	CH$_3$COCH$_2$C$_6$H$_5$	46.5
p-CHO—C$_6$H$_4$—OCH$_3$	32	C$_6$H$_5$COCH$_3$	0.8
o-CHO—C$_6$H$_4$—OH	60	C$_6$H$_5$COC$_2$H$_5$	1.7
m-CHO—C$_6$H$_4$—OH	208	C$_6$H$_5$COC$_3$H$_7$-n	1.1
p-CHO—C$_6$H$_4$—OH	13		
m-CHO—C$_6$H$_4$—CH$_3$	167		
p-CHO—C$_6$H$_4$—CH$_3$	97		

It is evident that the tendency towards cyanohydrin formation is greater in aldehydes than in ketones (C$_6$H$_5$CHO = 213, C$_6$H$_5$COCH$_3$ = 0.8) and is greater in aliphatic ketones than in aromatic ketones (CH$_3$COCH$_3$ = 33, C$_6$H$_5$COCH$_3$ = 0.8). Aliphatic aldehydes react so completely that the equilibrium is not easy to measure. Of course, when the reaction is carried out in a solvent, it is evident that the concentrations should be kept as high as possible.

For the gas-phase reaction of hydrogen cyanide with an aliphatic ketone, ΔH from bond energies is +0.5 kcal. For the liquid-phase reaction, ΔH, though somewhat larger, still is not far from zero. Since this is so small, the value for the reaction in aqueous solution is difficult to approximate, owing to the fact that the heats of solution of the components, all of which are not available, become important. However, when a strong acid such as nitric acid is used with sodium cyanide, the reaction is exothermic to the extent that a cooling bath is necessary when one is working with 1 mole, as in Experiment 41-1. This is due mainly to the ΔH of reaction of nitric acid with sodium cyanide.

The isolation of the cyanohydrin is easy if prepared from a ketone or aldehyde of five or more carbon atoms, for it largely separates as an oil when water is the solvent. Acetone cyanohydrin, however, is quite soluble, and, except when the volume of water is low and the resulting salt concentration is very high, ether extraction is necessary. The cyanohydrin of methyl ethyl ketone (Experiment 41-1) separates well from the salt solution. Generally the crude α-cyanohydrin need not be purified before conversion to the hydroxy acid, provided the opera-

tion is carried out without delay, since the cyanohydrin decomposes on standing. The hydrolysis is done in acid solution since a strong base converts an α-cyanohydrin into the original oxo compound. The acid concentration should be high, to insure a reasonable rate.

41.13 The Nitrile Synthesis. The preparation of β-hydroxy acids (method *b*) can be carried out with a chloro- or bromohydrin RCH(OH)-CH_2X and an alkali cyanide but is even slower than with an alkyl halide RCH_2X. The resulting β-cyanohydrin may be converted to the resulting β-hydroxy acid by acid or alkaline hydrolysis. In either case the hydroxy acid is in equilibrium with the unsaturated acid. See 41.17.

41.14 Reaction of Alpha-Halogenated Fatty-Acid Esters with Aldehydes or Ketones in the Presence of Zinc. The Reformatsky reaction method *c* is an excellent method of preparing a β-hydroxy acid. The reaction is carried out by mixing the carbonyl compound, halogenated ester, and zinc together with benzene as the solvent. The reaction is started by heating and then proceeds by itself. When the chloroester is used, copper powder must also be added to the mixture in order for the reaction to proceed. The ester may be converted to the acid by saponification, but care must be taken that the β-hydroxy acid does not dehydrate. See 41.17.

41.15 Oxidation of Glycols and of Hydroxy Aldehydes. In method *d* oxidation in aqueous solution can be accomplished by means of oxygen or air in the presence of platinum as a catalyst, or by dilute nitric acid. However, with this latter reagent there are many side reactions, and the product is difficult to purify. An excellent oxidizing agent which gives a smoother reaction is mercuric oxide in barium hydroxide solution. The commoner oxidizing agents such as permanganate and chromic acid are liable to carry the oxidation beyond the hydroxy-acid stage.

41.16 Reduction of Ketoesters. In method *e* reduction to the hydroxy ester may be accomplished by sodium amalgam in dilute alcoholic solution. The solution is kept from becoming too basic by buffering with aluminum sulfate or carbon dioxide. The hydroxy ester thus obtained then can be saponified to yield the acid. This is an excellent source of various α-substituted β-hydroxybutyric acids, since the ketoesters may be prepared from acetoacetic ester (Chapter 40).

41.17 Hydration of Unsaturated Acids. In method *f* hydration takes place in aqueous solution at elevated temperatures and is catalyzed by hydroxyl or hydrogen ions. Sulfuric acid is better than hydrochloric acid in the hydration, since there is the possibility of hydrogen chloride addition in the latter case. The reaction is reversible and

comes to an equilibrium. Therefore, the product must be separated from the unsaturated compound. The method is of value mainly for obtaining various β-hydroxy propionic, butyric, and isobutyric acids with alkyl substituents in the *alpha* position.

In the hydration of higher homologues of the type $R_2C{=}CR'COOH$ where R is greater than methyl, mixtures of hydroxy acids may result since an α,β-unsaturated acid may rearrange to a β,γ-unsaturated acid, especially in basic solution, which accelerates the double bond shift. The β,γ-acid may yield a γ-hydroxy acid as well as a β-hydroxy acid.

The reaction should be carried on at as low a temperature as possible since the equilibrium shifts to the side of unsaturation with rise in temperature, as in the hydration of olefins (Chapters 14 and 19). However, the rate usually is so low that heating is necessary. In the hydration of crotonic acid to β-hydroxybutyric acid in dilute aqueous solution, the equilibrium constant K is 5.0 at 90° and 3.4 at 110°.

$$CH_3CH{=}CHCOOH + H_2O \underset{}{\overset{H_3O^+}{\rightleftharpoons}} CH_3CH(OH)CH_2COOH$$

$$K = \frac{(CH_3CH(OH)CH_2COOH)}{(CH_3CH{=}CHCOOH)}$$
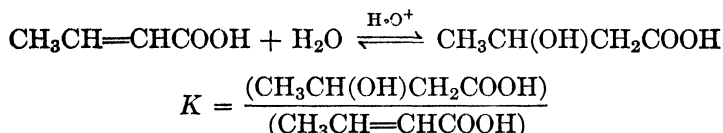
Side reactions are decarboxylation and polymerization. For this reason the yield of hydroxy acid passes through a maximum with time.

41.18 Reaction of Nitrous Acid with α-Amino Acids. Method f is of little value synthetically, since in general the hydroxy acids are more readily synthesized than are the amino acids (Chapter 42).

41.19 Isolation of Hydroxy Acids. The isolation and purification of hydroxy acids is complicated by their high solubility in water and by their tendency to decompose when heated. Those that possess high solubility in water and low solubility in ether (citric and tartaric acids) cannot be extracted from aqueous solution. Separation from soluble impurities often can be accomplished by precipitation as a sparingly soluble calcium or barium salt. This is decomposed by the addition of the metathetical amount of dilute sulfuric acid. The insoluble calcium or barium salt is removed, and the pure hydroxy acid is recovered by evaporation of the filtrate. Lead salts may be decomposed with hydrogen sulfide, or silver salts with a hydrohalic acid or with hydrogen sulfide.

The oxygen-to-carbon ratio in a hydroxy acid is an indication of the extractability by ether (refer to Chapter 6). As this ratio drops, the acid becomes more easily extracted from water solution. Thus α-hydroxy-α-methylbutyric acid $C_5H_{10}O_3$ (Experiment 41-1) can be extracted without much difficulty from the aqueous solution, but lactic

acid, $C_3H_6O_3$ requires continuous extraction. Tartaric acid $C_4H_6O_6$ and citric acid $C_6H_8O_7$ cannot be extracted.

Many hydroxy acids may be purified further by distillation at low pressure, as may lactic acid and α-hydroxy-α-methylbutyric acid (Experiment 41–1). The temperature of distillation must be kept low because of side reactions. These involve elimination of water, leading to the formation of lactides from α-hydroxy acids, unsaturated acids from *beta*, lactones from *gamma* and *delta*, and high-molecular-weight polyesters from hydroxy acids in which the hydroxyl radical is further away. Also, some polyester may be formed from an α-, β-, or γ-acid. Since all these reactions are catalyzed by strong acids, it is essential that the hydroxy acids be free of any strong acid before distilling.

Experiment 41–1   Preparation of α-Hydroxy-α-Methylbutyric Acid

Equip a 1-liter three-necked flask with a mechanical stirrer (a sealed stirrer is not necessary) and a thermometer which permits easy reading of the temperature (25° and lower; Note 1). The flask should be elevated so as to permit easy manipulation of a cooling bath. Measure out and cool 2.0 moles of concentrated c.p. nitric acid (take the density of the acid unless its concentration is definitely known). Place 2.1 moles of sodium cyanide (in powder or small granular form, Note 2) and 2.0 moles of butanone in the flask. Set a large-capacity cooling bath (Note 3) of ice and either salt or hydrochloric acid under the flask. Start the stirrer, add 150 g. of ice (Notes 4 and 5), stir for 1 or 2 minutes to allow some of the sodium cyanide to dissolve, and then add the nitric acid in portions of 10 ml. as rapidly as consistent with control of the temperature, which should be 20° or lower (Notes 6 and 7). Just before the last 30 ml. of the acid is added, remove the cooling bath so that the temperature will rise to 20 to 25° as the last of the acid is added. Continue the stirring for several minutes longer at 20 to 25° (Note 8).

Decant the liquid phases from any solid into a separatory funnel (500 ml.), and separate the two phases (Note 9; *Caution:* The aqueous phase should be poured down the sink in the hood, with a good stream of water following). The organic phase should not be acidic to moist litmus. If it is, shake it with 50 ml. of half-saturated sodium sulfate solution (Note 10). Put the organic phase in a 1-liter round-bottomed flask. Add with shaking sufficient concentrated hydrochloric acid (c.p. 37½%) to furnish 2.5 moles of hydrogen chloride. Then attach a reflux condenser fitted with an arrangement for absorbing evolved hydrogen chloride. The mixture should become warm from the heat

of reaction. Cool moderately if hydrogen chloride boils out at first, as the mixture becomes warm. Later, when the reaction has moderated, apply heat with a small flame, again taking care not to lose much hydrogen chloride. Finally, if much solid ammonium chloride has precipitated and bumping is bad, put a steam bath underneath. Continue heating for 7 hours.

Disconnect, add 100 ml. of water and 100 g. of anhydrous powdered sodium sulfate (Note 11), or, preferably, follow the procedure of Note 12. Mix well, add 200 to 400 ml. of ether, shake, let settle, and decant the ether phase into a 1-liter flask. Repeat with other 100-ml. portions of ether until a portion of the ether phase on evaporation leaves but little residue. Usually at least three extractions are necessary. Dry the ether extracts by shaking for several minutes with successive additions of powdered anhydrous magnesium sulfate, or other suitable drying agent until the solid picks up no more water. To diminish loss of product the solid before being discarded can be washed with ether.

Strip off the ether, using a 500-ml. Claisen flask (Note 13) and running in the dried extract (*Caution:* Note 14). After all the extract has been added, continue the distillation until the temperature is about 60° (Note 15).

Equip the flask for vacuum distillation (Figure 8–5), and have two similar flasks for receivers. Reduce the pressure to 100 to 150 mm., and distil off and collect separately any butanone. This should be redistilled for calculation of the yield later. After this has distilled (refer to Figure 8–2), change the receiver, reduce the pressure gradually to about 20 mm., and then heat the bath gradually to about 150° until hydroxy acid distils. Allow several milliliters of the product to distil over before again changing the receiver and collecting the product (Note 16). During the distillation it will be necessary to raise the bath temperature to drive over all of the acid (Notes 17, 18 and 19).

Calculate the percentage yield on two bases, that on the ketone taken, and that corrected for ketone recovered, which should first be redistilled. Take and record the melting point of the hydroxy acid (see Note 16). The yield can be increased by saponifying the boiler residue (Note 20).

Notes

1. If preferred, a dropping funnel may be attached, and the acid may be added gradually, instead of in portions, as directed. However, it then is not so easy to see whether or not the reaction is taking place.

2. *Caution:* See Experiment 37–1, Notes 1 and 2.

3. Preferably in a 2-gallon crock, so arranged that it can be lowered and moved to one side easily. The amount of ice this holds is sufficient.

4. Some water must be present initially for the reaction to proceed at a satisfactory rate below 25°.

5. The amount of water present is just about enough to dissolve the sodium nitrate formed. The volume of the aqueous phase must be kept low to minimize loss of cyanohydrin, which is *very* soluble in water, and to keep the salt concentration as high as possible. Sodium nitrate has a high solubility in water and salts out the cyanohydrin. Almost any combination that yields hydrogen cyanide and a salt highly soluble in water can replace sodium cyanide and nitric acid in this type of reaction. Sulfate ion and other bivalent negative ions usually salt out organic compounds better than does nitrate ion. The amount of water needed for dissolving the final inorganic salt can be estimated from the respective curve of Figure 2–1.

Three other satisfactory combinations are: (1) sodium (or potassium) cyanide and sulfuric acid, (2) sodium (or potassium) cyanide and sodium (or potassium) bisulfate, (3) sodium (or potassium) cyanide and sodium (or potassium) bisulfite.

Combination 1 is carried out as with nitric acid. The amount of acid can be varied, depending on the nature of the desired salt, that is, whether the neutral or acid sulfate. The acid should be diluted beforehand to at least 40 or 50% and added cold. Combination 2 is carried out similarly.

Combination 3 has the advantage that the aldehyde or ketone may be allowed to first form the bisulfite addition compound, and this, when slightly soluble, may be separated from the bulk of the aqueous solution. Then the cyanide solution is added.

6. With each addition of acid there is a temperature rise of 5 to 10°. This is largest at first, when the volume is the smallest. If stirring is rapid and the cooling bath is an efficient one, the addition of the nitric acid can be made quite rapidly, in 20 to 40 minutes.

7. If the temperature is too high, hydrogen cyanide may escape into the laboratory.

8. The yields are better if all the operations up to and including the addition of the hydrochloric acid (later) are carried out as rapidly as possible. The cyanohydrin is not very stable and darkens on standing.

9. Use the drawn-off water–acid phase to wash any salt left in the reaction flask, so as to recover more of the organic phase. If preferred, the mixture can be filtered (suction) from any solid, which can be washed with the aqueous phase, to wash out any organic phase on the solid. The crude cyanohydrin has much water dissolved in it. It should weigh about 230 g. The weight is increased a little (about 10 g.) by decreasing the original volume of water from 150 to 75 g., but this involves handling more solid and is hardly worth the trouble.

10. This serves to remove any dissolved nitric acid, which is detrimental in the next step. Of course, this operation is not necessary if the solution is not acidic or if the source of hydrogen cyanide was one of the combinations of Note 5. There is some loss of cyanohydrin in this operation, due to its great solubility in water. A saturated solution of sodium sulfate is not advised, since the cyanohydrin which dissolves in it causes the separation of some crystalline sodium sulfate.

11. This serves to remove most of the hydrochloric acid. If this is not done, the mutual solubilities of the aqueous and ether phases are so large that extraction is not satisfactory.

12. An alternative procedure, one that avoids increase in volume of the aqueous phase and also permits easier handling during the ether extraction, involves adding the 100 g. of powdered sodium sulfate to the reaction mixture, stirring vigorously for

10 to 15 minutes, and then filtering with suction. The salt cake, which should be *very well pressed,* can then be extracted with the ether which subsequently is used for extracting the aqueous phase.

13. A packed column is not necessary, because of the large separation in the boiling points. However, a short packing of 3 to 5 cm. length in the neck is advantageous. Be sure that the *side arm is wide,* to facilitate rapid distillation, once the lower-boiling impurities have been removed, and to minimize clogging.

14. Take the usual precautions when distilling ether. A microburner may be used for the early stages of the distillation.

15. This temperature is quite arbitrary, but waiting for the temperature to go up is a waste of time because butanone is subsequently distilled at reduced pressure (100 to 150 mm.).

16. Avoid collecting the first few milliliters with the main portion, for the impurity present lowers the melting point of the acid, which melts at 72.5° when pure. The melting point drops rapidly if the distilled acid is exposed to air, because of its high solubility in water.

17. Decomposition takes place at high temperatures yielding the lactide as one product. Therefore, do not increase the temperature above 200° unless necessary. Also, do not prolong the distillation unnecessarily, but carry it out as rapidly as feasible, once the correct boiling point is reached.

18. The corrected boiling point is 126° at 17 mm., and 105° at 7 mm. Boiling points at other pressures can be found from Figure 8-2. The yield is 60 to 65%.

19. Instead of distilling, the acid can be crystallized but only after all water has been removed at reduced pressure. Use about 2 liters of a mixture of ligroin (60–80°) and benzene (80°) in the ratio of about 3 to 1, and dissolve by heating under a reflux condenser. Take precautions against fire, because of the flammable nature of the solvent.

20. The boiler residue contains the lactide from which the hydroxy acid can be regenerated by heating with aqueous sodium hydroxide. This solution is then acidified and the hydroxy acid obtained as in the procedure already outlined.

Questions

1. To what is the deterioration of sodium or potassium cyanide due?
2. Why does the egg-sized product keep better?
3. What is the advantage of the high molal solubility of sodium nitrate?
4. Calculate the amount of water needed to dissolve the sodium nitrate at 20°.
5. Why is the cyanohydrin phase washed with aqueous sodium sulfate?
6. Explain why ΔH for the liquid-phase reaction of hydrogen cyanide with an aliphatic ketone is approximately 5 kcal. greater than for the gaseous reaction.
7. Why is the presence of nitric acid undesirable?
8. To what is the dark color of the hydrochloric acid solution due?
9. How does shaking with sodium sulfate solution remove hydrochloric acid?
10. Explain the action of aqueous sodium hydroxide on acetone cyanohydrin.
11. Why is it desirable to remove hydrochloric acid before extracting with ether?
12. How is change in pressure with temperature of boiling approximated?
13. By what other method might this acid be prepared?
14. How many stereoisomeric forms of the lactide are there?

Experiment 41-2   Properties of Hydroxy Acids

Carry out tests on lactic acid, tartaric acid, malic acid, and α-hydroxy-α-methylbutyric acid.   A tabulation of the results can be made, if desired.

A   PYROLYSIS.   Heat a small portion (0.5 to 1 g.) of the acid in a small test tube with a small flame.   Note any changes.

B   FERRIC CHLORIDE TEST FOR α-HYDROXY ACIDS.   Add a few drops of a water solution of ferric chloride (Note 1) to a few milliliters of a dilute water solution of the hydroxy acid in a test tube.   Compare the color produced with a blank test, using an equal volume of water.   Add dilute sodium hydroxide solution dropwise to each test tube.

C   COMPLEX FORMATION WITH CUPRIC ION.   To a few milliliters of a neutral solution of the sodium salt of the acid add a few drops of copper sulfate solution.   Compare with a blank test.   Add sodium hydroxide solution to each solution.

D   SOLUBILITY   Test the solubility of the acid (preferably in finely divided form) in water, methanol, ether, and gasoline.

E   REDUCING PROPERTIES.   Add a few drops of an aqueous solution of the sodium salt of the acid to the following, and warm slightly if no action is observed cold: (*a*) ammoniacal silver nitrate (Note 2), (*b*) aqueous permanganate, (*c*) aqueous dichromate acidified with sulfuric acid, (*d*) warm aqueous iodine (in potassium iodide), then drop by drop aqueous sodium carbonate to the solution containing both the hydroxy acid and iodine.

Notes

1. The ferric chloride should be quite dilute (faint straw color).
2. See Experiment 25–5, Note 3.

Questions

'   1. Why do hydroxy acids behave differently from monobasic unsaturated acids when heated?

2. What type of chemical change is associated with the color change with ferric and cupric ions?

3. Why does not a metallic hydroxide precipitate readily on the addition of hydroxide ions in B and C?

4. How do you account for the solubility behavior of the hydroxy acids?

5. Which substances give the iodoform reaction?

6. Write the formulas of the hydroxy acids used.

7. For which of these acids are optically active forms possible?

8. What is ΔH for the gas-phase reaction of hydrogen cyanide with an aliphatic aldehyde? aromatic aldehyde? aromatic ketone?

Chapter 42

AMINO ACIDS

The α-amino acids are the most important of the amino acids, because they constitute the building units of proteins, in which they are joined together by peptide linkages.

The α-amino acids can be prepared by those methods which are general for amino compounds and also by methods which are specific for α-amino acids. In the first group are (a) the reaction of an α-halogenated acid with ammonia (or an amine) and (b) the reaction of an ester of an α-halogenated acid with potassium phthalimide (the Gabriel synthesis). Among the methods that are specific for α-amino acids are: (c) the Strecker amino nitrile synthesis in which an aldehyde or ketone reacts with hydrogen cyanide and ammonia, (d) the azlactone synthesis, in which an aromatic aldehyde or ketone reacts with hippuric acid, (e) the hydantoin synthesis in which an aromatic aldehyde or ketone reacts with hydantoin, (f) the reaction of benzamidomalonic ester and an alkyl halide. In most of the methods outlined, the amino acid is obtained as a salt. Methods for obtaining the amino acid from the reaction mixture are discussed later.

(a) $\quad 2NH_3 + ClCH_2COOH \longrightarrow NH_2CH_2COOH + NH_4Cl$

(b, 1) $\quad C_6H_4(CO)_2NK + ClCH_2COOC_2H_5 \longrightarrow$

$$C_6H_4(CO)_2NCH_2COOC_2H_5 + KCl$$

$C_6H_4(CO)_2NCH_2COOC_2H_5 + 3KOH \longrightarrow$

$$C_6H_4(COOK)_2 + NH_2CH_2COOK + C_2H_5OH$$

$C_6H_4(COOK)_2 + NH_2CH_2COOK + 4HCl \longrightarrow$

$$C_6H_4(COOH)_2 + ClNH_3CH_2COOH + 3KCl$$

(b, 2) $\quad C_6H_4(CO)_2NK + BrCH(COOEt)_2 \xrightarrow{\text{heat}}$
potassium phthalimide

$$C_6H_4(CO)_2NCH(COOEt)_2 + KBr$$
phthalimidomalonic ester

$EtONa + C_6H_4(CO)_2NCH(COOEt)_2 \longrightarrow$

$$C_6H_4(CO)_2NCNa(COOEt)_2 + EtOH$$

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$$C_2H_5Br + C_6H_4(CO)_2NC(COOEt)_2 \xrightarrow{heat}$$
$$\underset{Na}{}$$

$$C_6H_4(CO)_2NC(COOEt)_2 + NaBr$$
$$\underset{C_2H_5}{}$$

ethyl phthalimidomalonic ester

$$4KOH + C_6H_4(CO)_2NCEt(COOEt)_2 \xrightarrow{heat}$$
$$C_6H_4(COOK)_2 + EtCNH_2(COOK)_2 + 2EtOH$$

$$3HBr + C_2H_5CNH_2(COOK)_2 \longrightarrow$$
$$C_2H_5C(NH_3Br)(COOH)_2 + 2KBr$$

$$C_2H_5C(NH_3Br)(COOH)_2 \xrightarrow{heat}$$
$$CH_3CH_2CH(NH_3Br)COOH + CO_2$$

(c, 1) $\quad (CH_3)_2CO + HCN \longrightarrow (CH_3)_2C(OH)CN$

$(CH_3)_2C(OH)CN + NH_3 \longrightarrow (CH_3)_2C(NH_2)CN + H_2O$

(c, 2) $\quad CH_3CHO + NH_3 \longrightarrow CH_3CH(OH)NH_2$

$CH_3CH(OH)NH_2 + HCN \longrightarrow CH_3CH(NH_2)CN + H_2O$

(c, 3) $\quad CH_3CHO + NH_4CN \longrightarrow CH_3CH(NH_2)CN + H_2O$

$(CH_3)_2C(NH_2)CN + 2H_2O + 2HCl \longrightarrow$
$$(CH_3)_2C(COOH)NH_3Cl + NH_4Cl$$

$CH_3CH(NH_2)CN + 2H_2O + 2HCl \longrightarrow$
$$CH_3CH(COOH)NH_3Cl + NH_4Cl$$

(d) $\quad C_6H_5CHO + H_2C\!-\!N\!=\!CC_6H_5 + Ac_2O \longrightarrow$
$$\underset{O=C\!-\!-\!-\!-\!O}{}$$

azlactone of hippuric acid

$$C_6H_5CH\!=\!C\!-\!N\!=\!C\!-\!C_6H_5 + 2AcOH$$
$$\underset{O=C\!-\!-\!-\!-\!O}{}$$

$$C_6H_5CH\!=\!C\!-\!N\!=\!CC_6H_5 + NaOH \longrightarrow$$
$$\underset{O=C\!-\!-\!-\!-\!O}{}$$

$$C_6H_5CH\!=\!C\!-\!NH\!-\!CC_6H_5$$
$$\underset{COONa \quad\ O}{}$$

sodium α-benzamidocinnamate

$$C_6H_5CH\!\!=\!\!\underset{\underset{COOH}{|}}{C}\!\!-\!\!NH\!\!-\!\!\underset{\underset{O}{\|}}{C}C_6H_5 \xrightarrow[\text{amalgam}]{\text{Na}}$$

$$C_6H_5CH_2\!\!-\!\!\underset{\underset{COONa}{|}}{CH}\!\!-\!\!NH\!\!-\!\!\underset{\underset{O}{\|}}{C}C_6H_5$$

$$C_6H_5CH_2\!\!-\!\!\underset{\underset{COONa}{|}}{CH}\!\!-\!\!NH\!\!-\!\!\underset{\underset{O}{\|}}{C}C_6H_5 + NaOH \longrightarrow$$

$$C_6H_5CH_2CH(NH_2)COONa + C_6H_5COONa$$
sodium α-amino-β-phenylpropionate

$$C_6H_5CH_2\underset{\underset{COONa}{|}}{CHNH_2} + C_6H_5COONa + 3HCl \longrightarrow$$

$$C_6H_5CH_2\underset{\underset{COOH}{|}}{CHNH_3Cl} + C_6H_5COOH + 2NaCl$$

(e) $$C_6H_5CHO + \underset{\underset{O=C-\!\!-\!\!-\!\!-NH}{|}}{H_2C\!\!-\!\!NH\!\!-\!\!CO} \longrightarrow$$
hydantoin

$$\underset{\underset{O=C-\!\!-\!\!-\!\!-NH}{|}}{C_6H_5CH\!\!=\!\!C\!\!-\!\!NH\!\!-\!\!CO} + H_2O$$
benzalhydantoin

$$\underset{\underset{O=C\!\!-\!\!-\!\!-NH}{|}}{C_6H_5CH\!\!=\!\!C\!\!-\!\!NH\!\!-\!\!CO} + 4HI + 2H_2O \longrightarrow$$

$$C_6H_5CH_2\underset{\underset{NH_2\cdot HI}{|}}{CH\!\!-\!\!COOH} + NH_4I + CO_2 + I_2$$
phenylalanine hydroiodide

(f) $$EtONa + \underset{\underset{NHCOC_6H_5}{|}}{HC(COOEt)_2} \longrightarrow \underset{\underset{NHCOC_6H_5}{|}}{NaC(COOEt)_2} + EtOH$$
benzamidomalonic ester

$$CH_3I + \underset{\underset{NHCOC_6H_5}{|}}{NaC(COOEt)_2} \longrightarrow \underset{\underset{NHCOC_6H_5}{|}}{CH_3C(COOEt)_2} + NaI$$

$$3HBr + H_2O + CH_3\underset{\underset{NHCOC_6H_5}{|}}{C}(COOEt)_2 \longrightarrow$$

$$CH_3\underset{\underset{NH_3Br}{|}}{C}(COOH)_2 + C_6H_5COOH + 2EtBr$$

$$CH_3\underset{\underset{NH_3Br}{|}}{C}(COOH)_2 \xrightarrow{\text{heat}} CH_3\underset{\underset{NH_3Br}{|}}{C}HCOOH + CO_2$$

<div align="center">alanine hydrobromide</div>

42.11 Ammonolysis of Alpha-Halogenated Acids. In method *a* the reaction is carried out by means of aqueous ammonia, which dissolves the halogenated acid, even if it is only slightly soluble in water, owing to salt formation. The ammonolysis reaction actually is between ammonia and the negative ion of the acid, for the halogen is more reactive in the ion than in the acid. In general, the reaction is carried out with bromo acids, since chloro acids are too unreactive. However, chloroacetic and α-chloropropionic acids are satisfactory. The former reacts satisfactorily in 2 days at 25° or in 4 hours at 60°. Chloropropionic acid reacts more slowly.

Side reactions lead to the formation of the corresponding secondary and tertiary amines, which in the ammonolysis of a haloacetic acid have the formulas $HN(CH_2COOH)_2$ and $N(CH_2COOH)_3$. These are the main reaction products, even when there are 4 moles of ammonia to one of haloacid. These side reactions generally are less extensive in the case of the higher α-bromoacids.

A large excess of ammonia is necessary to minimize the side reactions; for example, the yield of glycine is increased from 30 to 70% when the molal ratio of ammonia to chloroacetic acid is raised from 4 to 60. The side reactions may be less extensive in the case of higher acids; for example, α-bromo-isovaleric acid gives a 45% yield of DL-valine with 15 moles of ammonia.

The side reactions are minimized better by the addition of ammonium carbonate. Thus, in Experiment 42–1, a 70% yield of glycine results with only 6 moles of ammonia when 4 moles of ammonium carbonate are present. The increase in yield is believed to result from the formation of an intermediate compound which is unreactive with a second molecule of the halogenated acid, and which later is decomposed as the ammonia is removed by heating. This intermediate compound, a carbamate, is formed when the halogenated acid reacts with ammonium carbamate, present in ammonium carbonate.

$$(NH_4)_2CO_3 \rightleftharpoons NH_2COONH_4 + H_2O$$

$$NH_3 + NH_4OCONH_2 + ClCH_2COONH_4 \longrightarrow$$

$$NH_4OCONHCH_2COONH_4 + NH_4Cl$$

$$NH_4OCONHCH_2COONH_4 \xrightarrow{heat} NH_2CH_2COOH + 2NH_3 + CO_2$$
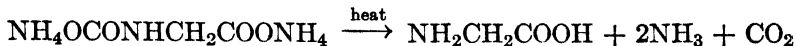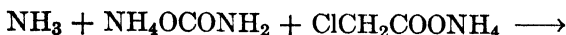
The higher α-bromoacids are prepared by bromination of the corresponding alkylmalonic acid. The resulting bromomalonic acid when heated decarboxylates to the desired bromoacid. The desired alkylmalonic acid is prepared by the standard malonic ester synthesis (Chapter 40). The steps involved, starting with an alkyl halide and sodiomalonic ester, are the following:

$$NaCH(COOEt)_2 \xrightarrow{RBr} RCH(COOEt)_2 \xrightarrow{KOH} RCH(COOK)_2 \xrightarrow{H_3O^+}$$

$$RCH(COOH)_2 \xrightarrow{Br_2} RCBr(COOH)_2 \xrightarrow{heat} RCHBrCOOH \xrightarrow{NH_3}$$

$$RCH(NH_2)COOH$$
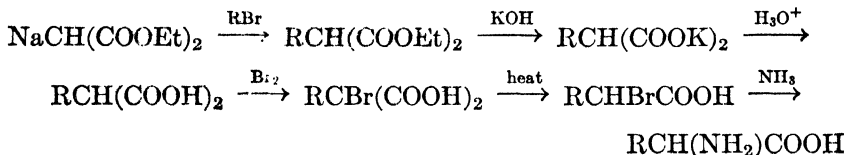
The reaction of chloroacetic acid with aniline to form N-phenylglycine (Experiment 42–2) is similar to the reaction of ammonia with this acid. The reaction is carried out at a higher temperature, however, because of the low solubility of aniline in water. The recovery of the product is easy, since it too is only slightly soluble in water. Sodium chloroacetate is used, rather than chloroacetic acid, for halogen replacement takes place much more rapidly with the ion:

$$ClCH_2COOH + NaOH \rightarrow ClCH_2COONa + H_2O$$

$$C_6H_5NH_2 + ClCH_2COONa \rightarrow C_6H_5NHCH_2COOH + NaCl$$
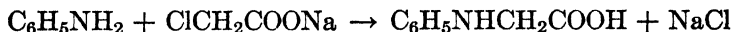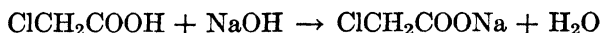
Side reactions are the formation of glycollic acid by the hydrolysis of chloroacetic acid or of N-phenylglycine. These reactions take place slowly at the boiling temperature and are more extensive, the higher the pH of the solution.

$$ClCH_2COONa + H_2O \rightarrow HOCH_2COOH + NaCl$$

$$C_6H_5NHCH_2COONa + H_2O \rightarrow HOCH_2COONa + C_6H_5NH_2$$
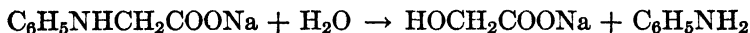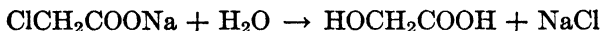
42.12   The Gabriel Synthesis. Method b, 1 is an extension of method a except that ammonia is replaced by potassium phthalimide and a halogenated acid by an ester of the acid. The acid itself would quickly convert potassium phthalimide to phthalimide. The reaction is carried out by heating the ester with solid potassium phthalimide and requires a high temperature.

42.13   The Phthalimidomalonic Ester Synthesis.   In method *b*, 2 ethyl phthalimidomalonate undergoes a typical malonic ester synthesis to yield an alkylated derivative which on hydrolysis and decarboxylation yields the desired α-amino acid.   Thus a large number of amino acids can be prepared by the use of alkyl halides.   Ethyl phthalimidomalonate is prepared by the reaction of ethyl bromomalonate with potassium phthalimide in the Gabriel synthesis.

42.14   The Strecker Synthesis.   Method *c* is an especially useful one for introducing both the amino and carboxyl groups into the molecule.   Aldehydes give much better results than ketones (see Table 41-1).   The amino nitrile can be prepared in three different ways: (1) by the reaction of ammonia with the cyanohydrin, which is formed from the aldehyde (or ketone) and hydrogen cyanide, (2) by the reaction of hydrogen cyanide with the amino alcohol (aldehyde ammonia) which is formed from the aldehyde and ammonia, (3) by the reaction of ammonium cyanide itself with the aldehyde.

In modification 1, the cyanohydrin reaction takes place quite rapidly (see Experiment 41-1) especially if the hydrogen cyanide is generated by the action of a strong acid on sodium or potassium cyanide.   The conversion of the cyanohydrin to the amino nitrile takes place more slowly.   In order to keep the concentration of the reactants high, organic solvents can be dispensed with and anhydrous ammonia can be passed directly into the crude cyanohydrin.   Often ether is used for the purpose of extracting the cyanohydrin from the reaction mixture, and this acts as a diluent.

In modification 2, an aldehyde ammonia is obtained usually in crystalline form when an aldehyde is treated with anhydrous ammonia. The aldehyde ammonia is formed also in solution by adding an aldehyde to aqueous or alcoholic ammonia.   The next step can be carried out by adding liquid hydrogen cyanide.   The use of an alkali cyanide and an acid is undesirable unless the amino acid is insoluble or only sparingly soluble.   Separating a soluble amino acid from the alkali salt is difficult.

In modification 3, the amino nitrile is obtained in one step by reaction with ammonium cyanide.   Usually, however, an ammonium salt and an alkali cyanide are used.   This has the disadvantage of introducing an alkali salt.

- The final step in the Strecker synthesis is the hydrolysis of the amino nitrile.   This should be done in acidic solution, since in aqueous solution a strong base decomposes the amino nitrile with formation of the original oxo compound, similar to the decomposition of a cyanohydrin (Chapter 41).   Usually, concentrated hydrochloric acid is used.

42.15 The Azlactone Synthesis. In method *d* benzaldehyde or other aromatic aldehyde condenses with the azlactone of benzoylglycine (hippuric acid) or of acetylglycine, when heated with acetic anhydride. The starting material may be also hippuric acid or acetylglycine, since these are converted into their azlactones when heated with acetic anhydride.

$$H_2C—NH—COC_6H_5 \rightleftharpoons H_2C—N=C—C_6H_5 \xrightarrow{Ac_2O}$$

$$O=C—OH \qquad\qquad O=C—OH \; O—H$$

lactam form   lactim form

$$H_2C—N=C—C_6H_5$$

$$O=C————O$$

hippuric acid   azlactone
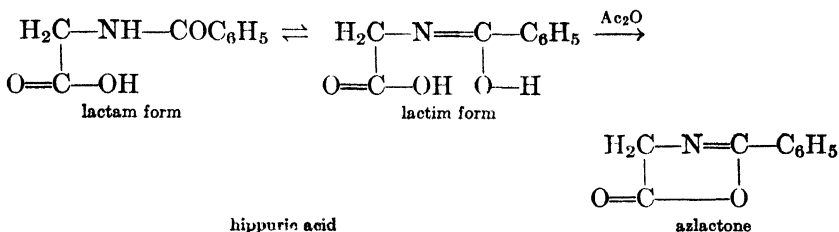
The condensation product with benzaldehyde is the azlactone of α-benzamidocinnamic acid. When this is warmed with aqueous base, the product is sodium α-benzamidocinnamate, formed by the opening of the azlactone ring. The double bond can be reduced by sodium amalgam to yield a salt of benzoylphenylalanine. This can be saponified to the sodium salt of phenylalanine by boiling with aqueous sodium hydroxide.

Acidification of the reaction mixture yields benzoic acid and a salt of the amino acid. The former is easily removed by filtration, extraction, or steam distillation. However, it is better to hydrolyze benzoylphenylalanine with aqueous hydrochloric acid, since then no metallic ions are present. The azlactone can be converted directly into phenylalanine hydroiodide, by heating with concentrated hydriodic acid and phosphorus. This brings about reduction, opening of the ring, and removal of the benzoyl group.

42.16 The Hydantoin Synthesis. In method *e* hydantoin is condensed with an aldehyde, for example furfural, piperonal, benzaldehyde, salicylaldehyde, anisaldehyde, under conditions similar to the condensation with hippuric acid. Benzaldehyde, for example, yields benzalhydantoin. The next step is the reduction of the double bond. This can be accomplished by sodium amalgam, hot hydriodic acid, or ammonium sulfide in a sealed tube at 150°. Benzalhydantoin is converted into benzylhydantoin. The last step is the opening of the hydantoin ring by the hydrolysis of all amide linkages, thus splitting out a molecule each of ammonia and of carbonic acid. This can be accomplished by heating with aqueous acids or bases, or by ammonium sulfide at 150°. Benzalhydantoin yields phenylalanine.

Thus the last two steps can be carried out in one operation by heating with hydriodic acid, or with ammonium sulfide at 150°. Since the reduction reaction is much more rapid than the hydrolysis reaction when hydriodic acid or ammonium sulfide is used, it is possible to obtain either the saturated hydantoin or the final amino acid. In Experiment 42–3 phenylalanine is obtained by heating with hydriodic acid and red phosphorus for 8 hours. The latter is the essential reducing agent, for it reacts with iodine, regenerating hydriodic acid.

$$3I_2 + 2P + 6H_2O \rightarrow 6HI + 2H_3PO_3$$
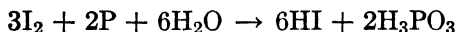
Hydantoin is formed by ring closure of hydantoic acid when it is evaporated to dryness with hydrochloric acid.

$$H_2NCONHCH_2COOH \xrightarrow[\text{HCl}]{100°} \begin{array}{c} H_2C-NH-C=O \\ | \quad\quad\quad | \\ O=C-\!\!\!-\!\!\!-\!\!\!-NH \end{array} + H_2O$$

hydantoic acid   hydantoin
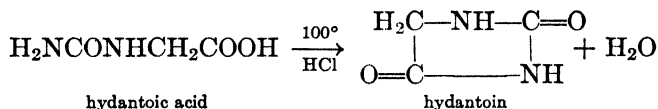
The reaction takes place also in boiling glacial acetic acid containing sulfuric acid, as in Experiment 42–3.

Hydantoic acid, ureidoacetic acid, can be obtained easily by heating urea and sodium aminoacetate in aqueous solution, and then adding acid, as in Experiment 42–3.

$$H_2NCONH_2 + H_2NCH_2COONa \rightarrow H_2NCONHCH_2COONa + NH_3$$

$$H_3O^+ + H_2NCONHCH_2COONa \rightarrow$$

$$H_2NCONHCH_2COOH + Na^+ + H_2O$$
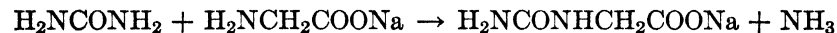
Other convenient methods are: the reaction of nitrourea with sodium aminoacetate,

$$H_2NCONHNO_2 + NH_2CH_2COONa \rightarrow$$

$$H_2NCONHCH_2COONa + N_2O + H_2O$$

and the reaction of potassium cyanate with glycine

$$K^+ + N=C=O^- + H_2NCH_2COOH \rightarrow H_2NCONHCH_2COO^- + K^+$$

42.17 The Benzamidomalonic Ester Synthesis. Method f is similar to the phthalimidomalonic ester synthesis. Here also alkyl halides can be used. This method also has the advantage that the formation of secondary amines is not observed. The substituted benzamidomalonic ester can be converted easily into the hydrobromide of

the desired amino acid by heating with hydrobromic acid, for in one operation the compound undergoes hydrolysis, and the resulting substituted malonic acid undergoes decarboxylation.

In the preparation of ethyl benzamidomalonate (benzamidomalonic ester) ethyl nitrosomalonate, easily obtained by the reaction of sodiomalonic ester with butyl nitrite, is reduced with hydrogen in the presence of Raney nickel to ethyl aminomalonate. This is benzoylated with benzoyl chloride in the presence of water and pyridine.

$$C_4H_9O-N=O + NaHC(COOEt)_2 \longrightarrow$$

$$NaO-N=C(COOEt)_2 + C_4H_9OH$$

$$H_2SO_4 + NaO-N=C(COOEt)_2 \longrightarrow$$

$$O=N-CH(COOEt)_2 + NaHSO_4$$
<center>nitrosomalonic ester</center>

$$2H_2 + O=N-CH(COOEt)_2 \xrightarrow[\text{pressure}]{\text{Ni}} H_2N-CH(COOEt)_2 + H_2O$$

$$Py + C_6H_5COCl + H_2N-CH(COOEt)_2 \longrightarrow$$

$$C_6H_5CO-HN-CH(COOEt)_2 + PyHCl$$
<center>benzamidomalonic ester</center>
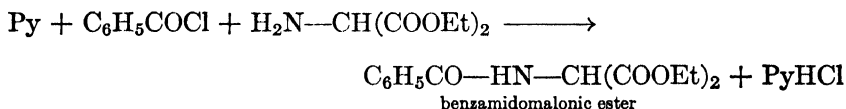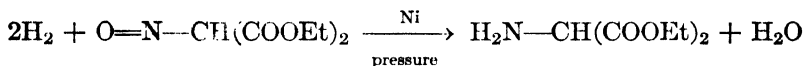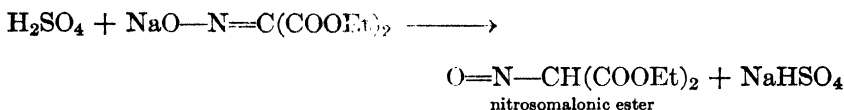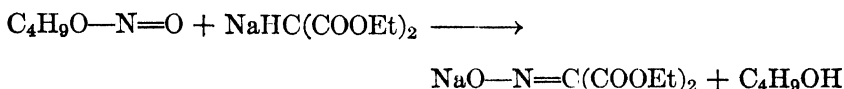
42.18   Isolation of Free Amino Acids. The amino acids usually are obtained in aqueous solutions which also contain soluble inorganic salts. Moreover, they generally are in the form of salts with hydrohalic acids, as in methods *b*, *c*, *d*, *e*, and *f*. Those amino acids which are slightly soluble in water at their isoelectric points can be separated easily from their reaction mixtures by proper adjustment of the *pH*.

Many soluble amino acids form slightly soluble salts, for example copper salts. The amino acid can be recovered from its copper salt by suspending this in water, passing in hydrogen sulfide, filtering from the insoluble copper sulfide, and evaporating the filtrate.

When a soluble amino acid is in the form of a hydrohalide salt and no other salts are present, the halide ion can be precipitated by adding the calculated amount of silver oxide. The silver halide is removed by filtration and the fitrate is evaporated to dryness or to a small volume, preferably under reduced pressure. In case ammonium halides are present also, the amount of silver oxide added should be just enough to precipitate all halide ion. The free ammonia must be removed by heating before filtering off silver halide; otherwise, some silver compound remains in solution in the form of an ammonia complex.

In case an ammonium halide is present and the amino acid is sparingly soluble in methanol, the aqueous solution of the amino acid and ammonium salt is evaporated to dryness, and the ammonium salt is extracted out of the residue by digesting with aqueous methanol, 90% methanol, as in the purification of glycine (Experiment 42–1).

Amino acids in general should be dried at room temperature or with gentle heating. If too strongly heated, amino acids form so-called anhydrides by elimination of water.

Experiment 42–1   Preparation of Glycine

In a 1-liter round-bottomed flask (distilling flask, in case evaporation is to be done at reduced pressure), heat *slowly* on a water bath, until the temperature reaches 55°, 2 moles of ammonium carbonate (Note 1) with 50 to 150 ml. of pure water (Note 2) and an amount of concentrated aqueous ammonia that furnishes 1.5 to 3.0 moles of ammonia. Cool to room temperature or lower, so as to minimize loss of ammonia during the next operation, and with thorough mixing (swirling) add in several portions 0.50 mole of chloroacetic acid (Note 3) dissolved in 50 ml. of water.

Maintain at a temperature of 60° for 4 hours (Notes 4 and 5). Evaporate according to Note 6 or Note 7, or at reduced pressure, as follows. Attach a capillary-air inlet tube (refer to Chapter 8), a condenser, and a 1-liter receiver half full of water. With the bath at 60° or lower, distil at reduced pressure, frequently mixing the receiver contents thoroughly, so as to dilute the lighter distillate, and recharging after much ammonia has accumulated (Note 8). Continue until little or no liquid remains. The residue should be colorless.

Dissolve the dry residue in 100 ml. of water at 70° to 75°, and filter the solution if not clear (the temperature should be raised, to prevent crystallization while filtering). Cool to 70°, add 350 ml. of methanol, and mix thoroughly. Let stand 0.5 to 1 day, and then collect the solid by suction filtration.

Extract most of the impurities from the crude glycine (Note 9) by stirring for 1 or 2 hours with 150 ml. of 90% (by volume) methanol, filter, and repeat (Note 10). Calculate the yield of glycine (Note 11).

Unless the product gives a negative test for chloride ion (Note 12), purify by dissolving in 50 ml. of hot water, adding about 1 g. of decolorizing carbon if the solution is colored, filtering and adding 150 ml. of methanol. Let stand several hours, collect the solid by suction filtration, and wash with three 10-ml. portions of methanol. The product should give a negative test for chloride ion (Notes 12 and 13).

Notes

1. The ordinary form is a monohydrate. See discussion regarding the importance of ammonium carbonate. Heating at 50° to 60° for about 0.5 hour before adding the chloroacetic acid is desirable, in order to promote the formation of ammonium carbamate. Take care that loss of ammonia is not excessive.

2. The smaller amount if 1.5 moles of ammonia is taken; the larger amount if 3 moles. The latter is preferred if Note 5 is followed.

3. Chloroacetic acid is very hygroscopic and thus seldom is 100% pure. It should be redistilled just before use (air condenser, hood).

4. This can be done conveniently by means of an oil bath (light oil) resting on an electric hot plate at "low" heat. This usually will maintain the oil bath at a temperature of about 60°. If this is too hot, raise the oil bath a short distance above the hot plate (actual manipulation is easier if the hot plate is lowered), or insert asbestos board between.

5. Instead of being maintained at 60° for 4 hours, the mixture may be allowed to stand at room temperature for 48 hours, with occasional agitation if ammonium carbonate separates. Because of the lower solubility the larger volume is desirable.

6. Raise the bath temperature to 80°, and let the solution evaporate until the volume is about 100 ml. This takes 12 to 24 hours. Filter hot if not clear, cool to 70°, and add the 350 ml. of methanol.

7. At the hood heat over a flame so as to give fairly rapid boiling. Agitate vigorously and continuously to minimize charring. Continue until the boiling temperature reaches 112°. Some darkening takes place. Heat with about 1 g. of decolorizing carbon, and filter while hot. The volume of the filtrate should be about 100 ml. Cool to 70°, and then add 350 ml. of methanol. This modification is the most rapid, but the product is not so white as in the other two modifications.

8. It is desirable to keep the partial pressures of ammonia and water vapor in the receiver as low as possible; otherwise, the pressure in the distilling flask will not approach that obtainable by the pump (refer to 8.24 and 8.27).

9. This crude glycine contains ammonium chloride and the ammonium salts of the acids resulting from further reaction with chloroacetic acid, namely, $HN(CH_2COOH)_2$ and $N(CH_2COOH)_3$.

10. The solubility of glycine is 0.3% in 99.5% methanol and 0.6% in 80% (by volume) methanol. The latter value rises to 1.38% in the presence of an equivalent amount of ammonium chloride. This is increased also by the presence of the compounds mentioned in Note 9. The solubility of ammonium chloride at 25° in 100% methanol is 3.7 g. per 100 g. and in 80% (by weight) methanol is 7.2 g. per 100 g.

11. The yield of glycine, containing about 0.2% ammonium chloride, is 70 to 75%. After recrystallization, the yield of chloride-free glycine is 60 to 65%.

12. Carry out the test by dissolving in a minimum volume of 1 N nitric acid.

13. This experiment is based on work by Cheronis and Spitzmueller, *Jour. Org. Chem.*, 6, 349 (1941).

Questions

1. Why is ammonium carbonate added to the reaction mixture?

2. What rapid reaction takes place when chloroacetic acid is added to the other reactants?

3. Write the equations for the reactions leading to the formation of acids other than aminoacetic acid.

4. How may the formation of these acids be minimized?

5. What objection is there to having the pressure in the flask much above that obtainable by the pump, when carrying on the evaporation at reduced pressure?

6. List all of the compounds present in the reaction mixture just before the ammonia is removed by evaporation.

7. Which α-amino acid is obtained when ethyl alcohol is the starting material for: (a) the Gabriel synthesis, (b) the Strecker synthesis, (c) the benzamidomalonic ester synthesis?

Experiment 42–2   Preparation of *N*-Phenylglycine

In a two- or three-necked 0.5-liter flask provided with a separatory funnel and a reflux condenser place about 50 ml. of water and 0.3 to 0.6 mole of aniline (Note 1). Heat to refluxing temperature, and add 0.20 mole of redistilled chloroacetic acid (Note 2). This may be added as an aqueous solution (use about 50 ml. of water) or as a solution of the sodium salt made by neutralizing the acid with cold aqueous sodium hydroxide (Note 3). The solution of the acid or the salt may be added rapidly or slowly (Note 4). After all is added, continue the refluxing for 10 to 20 minutes (Note 5). During this time slowly add 0.2 mole of sodium hydroxide solution, in case the acid was used initially, not the salt.

Steam-distil (refer to Section 10.2), passing in steam as rapidly as feasible until all aniline is removed and heating with a flame so as to hold the volume of the solution close to 0.1 liter. As soon as the rate of aniline removal becomes small, as shown by the distillate becoming one phase, run in aqueous sodium hydroxide slowly until the amount added is sufficient to convert all *N*-phenylglycine to the sodium salt (Note 6). Continue the steam distillation until a portion of the distillate is essentially free of aniline (Notes 7 and 8). About 0.4 to 0.5 liter of a one-phase distillate will be required.

Cool the liquid quickly, filter if not clear, and precipitate *N*-phenylglycine by addition of hydrochloric acid to a blue Congo red end point or to a pH of 2 to 3. Cool in an ice bath, collect by suction filtration, dry completely, determine the yield at this step and take the melting point.

Recrystallize from aqueous ethanol, not over 50% ethanol. Determine yield and melting point (Note 9).

Notes

1. The side reaction to form a tertiary amino compound is diminished by having aniline in excess. The melting point of the crude product can be as high as 122° with a 300% excess. With a 100% excess it is lower.

2. Chloroacetic acid is hygroscopic. If the melting point is low (the usual α-form melts at 61.2°), distil the acid (*hood*). An air condenser is recommended (refer to 7.21).

3. Owing to the greater reactivity of the sodium salt the mixture should be kept cold during the neutralization process; otherwise, hydrolysis may be extensive.

4. Slow addition, over a period of 10 to 20 minutes, seems to diminish the side reaction mentioned in Note 1.

5. The reaction proceeds with reasonable rapidity. Crude yields have been as high as 90% with only 15 minutes refluxing.

6. Unless some extra base is added, aniline remains behind, probably because of salt formation. The base should not be added too rapidly; otherwise, there may be decomposition of *N*-phenylglycine by hydrolysis in strongly basic solution (refer to 42.11).

7. This may be tested by adding bromine water, which gives a precipitate of tribromoaniline.

8. The melting point of the crude product is better if aniline is well removed. Moreover, purification by crystallization also is easier.

9. Yield of crude product (m.p. 115–118°) 70 to 90%, and of recrystallized product 60 to 80%. This should melt at 120–122°. Sometimes it melts at 125°. The melting point of pure *N*-phenylglycine is 127°, and its K_a value is 3.8×10^{-6}. It is used in Experiment 44-2, for preparing indigo.

Questions

1. What amide could be formed by a side reaction?

2. What conditions would be favorable for its formation?

3. What side reaction is minimized by having aniline in excess?

4. Does the organic compound formed in this side reaction interfere with the recovery of *N*-phenylglycine?

5. What reaction takes place when an aqueous solution of chloroacetic acid is heated?

6. How does the rate of this reaction compare with the rate of a similar reaction involving sodium chloroacetate?

7. Is either one of the reactions in Questions 3 and 5 promoted or hindered, relative to the main reaction in this preparation, by increasing the volume of water?

8. Does the organic compound formed in either of these reactions interfere with the recovery of *N*-phenylglycine? Explain.

9. How much water is needed to keep in solution the sodium chloride formed in this experiment?

10. How does an aqueous solution of *N*-phenylglycine affect litmus?

11. What is the main impurity in the product?

Experiment 42–3　Preparation of DL-β-Phenylalanine

HYDANTOIC ACID (Note 1). In a flask equipped with an efficient reflux condenser and thermometer reaching well to the bottom, dissolve 0.5 mole of sodium hydroxide in 75 ml. of water (Note 2). Add first 0.50 mole of glycine and then 1.0 mole of urea with thorough mixing (Note 3). Add several large boiling chips (Note 4), and heat rapidly to boiling with a bare flame. Note the temperature, which should be about 113°, and adjust the flame so as to obtain a good rate of reflux, 2 or 3 drops per second. Take readings at intervals of about 10 minutes. Tabulate the readings neatly in the notebook.

After about 1 hour the temperature should be close to 110°. Observe essentially continuously from this point on. A white solid should appear in the cold dry section of the condenser about the time 110° is reached. Continue heating for 5 or 10 minutes after the solid appears. Continued heating beyond this point usually causes a drop in the yield (Note 5). Cool to about 65° (Note 6).

Measure out an amount of concentrated hydrochloric acid that contains 0.50 mole of hydrogen chloride. Add about 90% of the acid in portions, cooling to prevent much rise in temperature. Cool to about 5°. Add the rest of the acid in small portions to a blue Congo red end point, or until the pH of the liquid is 2 to 3, taking more if necessary. Let stand near 0° for about 0.5 hour with frequent shaking, or stir mechanically for about 10 minutes, to promote crystallization. Collect by suction filtration, wash three times with 10 ml. portions of cold water, and allow to dry *completely*. Calculate the percentage yield, and determine the melting point (Note 7).

BENZALHYDANTOIN (Note 8). Equip a two-necked 500-ml. flask with a thermometer reaching well to the bottom and with a reflux condenser to which is attached an exit tube for collecting and measuring any evolved gas (Note 9). Use air-tight rubber connections. In the flask, disconnected, thoroughly mix 75 to 100 ml. glacial acetic acid (Note 10) and 10 ml. of concentrated sulfuric acid (Note 11). Add 0.30 mole of *thoroughly dried* hydantoic acid and 0.30 mole of acetic anhydride. Dissolve the solid by heating to about 70° to 80° with continuous swirling, so as to effect complete solution at this temperature (Note 12). Connect the condenser, and heat to about 100° in an oil or wax bath, taking care that gas evolution is only slight. If extensive, lower the temperature a little. During the course of about ¼ hour, gradually bring the temperature to about 120°, being careful that gas evolution is not extensive. Maintain at refluxing temperature for 0.5 hour. Record the volume of evolved gas here and at the next step. The amount should not exceed 0.1 mole, all told.

Cool somewhat, add 0.7 to 0.9 mole of finely ground *freshly fused* anhydrous sodium acetate (refer to Experiment 13–1) and a 10% excess of freshly distilled benzaldehyde (Notes 13 and 14). Heat for 2.5 to 4 hours at gentle and steady reflux. Allow to cool somewhat, and cautiously add about 50 ml. of water (or wash out the flask with the 50 ml.; Note 15). Cool to about 0°.

Agitate frequently to promote crystallization, and collect by suction filtration without needless delay (Note 16). After the solid is well pressed out, wash first with about 20 ml. of chilled alcohol and then with about 20 ml. of chilled water (Note 17). Recrystallize as soon as possible from alcohol. After drying thoroughly, determine melting point, and calculate the percentage yield (Note 18).

PHENYLALANINE. Heat for 8 hours under a reflux condenser 0.05 mole of benzalhydantoin with 50 ml. of hydriodic acid (sp. gr. 1.7, 57% by weight) and with sufficient red phosphorus to furnish about 50% excess over the amount necessary to reduce the double bond (Note 19). Remove phosphorus by suction filtration of the hot liquid through asbestos or through a sintered glass plate (Notes 20 and 21). Cool to 0°, and allow benzylhydantoin to crystallize completely, but do not allow the mixture to stand too long, for then phenylalanine hydroiodide crystallizes. Remove benzylhydantoin by suction filtration (Note 22) or, preferably, follow the procedure of Note 21.

Precipitate DL-phenylalanine by the cautious addition of concentrated ammonium hydroxide to neutrality. After crystallization is complete, collect the solid by suction filtration (Note 23), wash carefully with cold water until essentially free of iodide ion, and dry thoroughly. Take the melting point, and calculate the percentage yields from benzalhydantoin, hydantoin, and glycine (Note 24).

Notes

1. Much ammonia is evolved in this experiment. It is desirable that it escape freely. In case contamination of the laboratory air is undesirable, set up the apparatus in the hood. The condenser must have good capacity so that the upper half will remain dry (refer to 7.23).

2. The data have been established for this particular amount of water, which is close to the minimum, if the product is not to be needlessly contaminated.

3. An excess of urea is necessary for obtaining a good yield on the basis of glycine. A larger excess gives a somewhat higher yield.

4. Vigorous boiling is essential in order to boil out the ammonia as it is formed. The boiling chips should be large (about 1 cm.), so that they will stay at the bottom of the flask. The temperature is markedly lowered by dissolved ammonia.

5. Heating for 0.5 hour longer causes a drop in the yield of about 5%.

6. Sodium hydantoate separates if the reaction mixture is cooled much below this point.

7. Yield is 75 to 80% of product melting at 156–159°. Pure hydantoic acid melts at 180°.

8. In this operation two reactions are carried out, namely, conversion of hydantoic acid to hydantoin, and condensation of benzaldehyde with hydantoin to form benzal-hydantoin. The first reaction is catalyzed by a strong acid, the second by sodium acetate.

9. Formation of carbon dioxide is a troublesome side reaction and accounts for the drop in yield.

10. This amount is needed to dissolve the sodium acetate added at a later step. The decarboxylation reaction is more extensive if the sodium acetate is not dissolved. The smaller volume is about the minimum. The larger the volume, the lower is the boiling temperature of the solution.

11. The reaction proceeds more slowly with a smaller amount of acid.

12. Decarboxylation is worse at a higher temperature if some of the hydantoic acid remains undissolved.

13. With the larger amount of sodium acetate 2.5 hours' heating is sufficient. However, decarboxylation is then more difficult to control. The amount of sodium acetate should be sufficient to provide 1.5 moles of sodium acetate per mole of hydantoin, allowance being made for any reacting with sulfuric acid.

14. Benzaldehyde oxidizes rapidly on exposure to air.

15. Water is added to prevent crystallization of sodium acetate at the lower temperature and to decrease the solubility of benzalhydantoin. More should not be added; otherwise, impurities are thrown out of solution.

16. On standing in contact with acetic acid, cis-benzalhydantoin (m.p. 223–224°, with slight effervesence) slowly changes to trans-benzalhydantoin (m.p. 246°). At the refluxing temperature the equilibrium favors the cis isomer. On standing overnight at room temperature much trans isomer is formed. This may be due in part to a shift in the position of equilibrium or to the lower solubility of the trans isomer.

17. Alcohol removes much of the organic impurities and water removes much of the sodium acetate. Benzalhydantoin is soluble, 2 to 3 g. per 100 ml. of alcohol at 0°.

18. The yield is 60% of product melting at 220–230°. Some trans isomer can be isolated from the reaction mixture. Benzalhydantoin is yellow. It is only slightly soluble in boiling water, moderately soluble in alcohol, readily soluble in glacial acetic acid. It dissolves in dilute aqueous alkali from which it is precipitated unchanged by acetic or hydrochloric acid.

19. If the volume of acid is decreased, a longer heating time is required. The volume of acid may be increased, but, unless it is to be removed later by distillation at reduced pressure, more phenylalanine will be lost later, owing to solubility (see Note 24).

20. Be sure to clean the sintered plate thoroughly. Reverse flow of water under pressure may be sufficient to remove the phosphorus. If not, heat with nitric acid, to oxidize the phosphorus.

21. The loss of phenylalanine due to solubility can be minimized by removing most of the acid by distillation under reduced pressure with bath temperature at 100° or lower (refer to Chapter 8). Dissolve the residue in about 50 ml. of hot water, filter hot, allow benzylhydantoin to crystallize at 0°.

22. The amount of crude benzylhydantoin is about 15%. This can be decreased by heating for a longer time. To obtain a good yield of benzylhydantoin, heat for 1 hour only. Benzylhydantoin melts at 190° (185° in a sealed tube.)

23. Keep the filtrate separate. Divide into 2 parts; add a little acid to one and a little ammonia to the other to see if any phenylalanine will separate.

24. Phenylalanine melts at 283° with decomposition. It is soluble in water, 1.42 g. per 100 g. at 25°. The yield is 80% in this step, provided the hydriodic acid had been largely removed by distillation.

Questions

1. Why is the addition of sodium hydroxide desirable in the preparation of hydantoic acid?

2. Why not add more sodium hydroxide?

3. What would be the main contaminant of the hydantoic acid if the amount of water was much lower?

4. Would potassium hydroxide be as satisfactory as sodium hydroxide?

5. What solid collects in the reflux condenser?

6. What is a possible explanation of the continued drop in the temperature of the boiling liquid?

7. Why should the yield drop if the heating is continued beyond this point?

8. Explain why it is desirable to bring the mixture to a pH of 2 to 3 when precipitating hydantoic acid.

9. Explain why the amount of hydrochloric acid required exceeds 0.5 mole.

10. How is hydantoic acid named as a derivative of acetic acid?

11. What is the main impurity or impurities in the hydantoic acid?

12. What other reagents may be used for converting glycine to hydantoic acid?

13. What methods are available for converting hydantoic acid to hydantoin?

14. What functional groups are present in hydantoic acid?

15. How many reactions are involved in the conversion of hydantoic acid to benzalhydantoin?

16. What organic impurities are removed by washing with alcohol?

17. Why should recrystallization of benzalhydantoin be done without delay?

18. How many reactions are involved in the conversion of benzalhydantoin to phenylalanine hydroiodide?

19. What is the sequence of these reactions?

20. Why not remove phosphorus by filtering through filter paper?

21. What compound of phosphorus is formed?

22. Why does the addition of ammonia cause the precipitation of phenylalanine?

23. Why not add an excess of ammonia?

24. Can alanine be precipitated this way?

25. What is the maximum yield of benzalhydantoin possible, if the amount of gas evolved is taken into account?

Experiment 42–4   Properties of Amino Acids

A NINHYDRIN COLOR TEST FOR α-AMINO ACIDS. Dissolve about 5 mg. of glycine or other amino acid in 2 ml. of water. To half of this add a few drops of ninhydrin (triketohydrindene hydrate) solution, and heat in a boiling-water bath for 10 to 15 minutes. If the color is intense, repeat the test on a still less concentrated solution. Repeat until the limit of the test is reached (Note 1).

B XANTHOPROTEIC REACTION (Note 2). To very small amounts (1 mg. or less) of phenylalanine, alanine, and tyrosine, add 1 drop of concentrated nitric acid. After a few minutes, add a few drops of concentrated ammonium hydroxide solution.

C TEST FOR SULFUR (Note 3). In a small (3-inch) test tube add 1 or 2 drops of an aqueous solution of a lead salt and then, drop by drop, a solution of sodium hydroxide until the precipitate has dissolved. Then add a small amount (1 mg. or less) of cystine or cysteine. Set the tube in hot water for a few minutes.

D OXIDATION OF CYSTEINE (Note 4). To a small amount of cysteine (1 or 2 mg.) dissolved in a few drops of water, add a few drops of a dilute solution of iodine in potassium iodide (straw color). Let stand a few minutes. If color disappears, add more solution, not so dilute. Describe the results.

Notes

1. The color results from a series of reactions which involve (1) reduction of triketohydrindene to hydroxydiketohydrindene, (2) condensation of these two compounds with ammonia, which is liberated from the amino acid during the first reaction, to form diketohydrindylidene–diketohydrindamine, and (3) salt formation of this, as the enol form, with ammonia or other organic base. The negative charge of the anion can appear at any of the four oxygen atoms, as the result of resonance. This is the cause of the intense color. Ninhydrin gives about the most delicate of all

hydroxydiketohydrindene   triketohydrindene

diketohydrindylidene-diketohydrindamine   anion
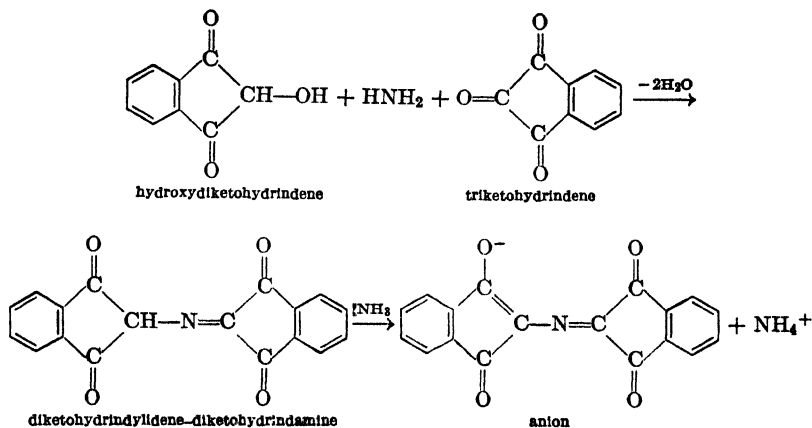
tests for the presence of the α-amino group, not only in the acids themselves but also in proteins.

2. This is a test for aromatic nuclei which undergo nitration readily (tyrosine and tryptophane). Phenylalanine is not nitrated easily. Proteins that contain these amino acid residues show the same color change.

3. This is a test for the disulfide and sulfhydryl groups, —S—S— and —S—H, respectively. These are the characteristic groups of cystine and cysteine, respectively. Proteins containing these amino acid residues give positive tests.

4. This is a test for the sulfhydryl group.

Questions

1. Write the formulas of glycine, alanine, phenylalanine, tyrosine, tryptophane, cystine, and cysteine.

2. What do you estimate to be the limiting concentration of the amino acid which gave the test with ninhydrin?

3. What is the reaction of tyrosine and tryptophane with nitric acid?

4. Why does the addition of ammonia change the color produced by nitric acid? Compare with o- or p-nitrophenol and ammonia.

5. What is the reaction when the white precipitate in C dissolves in sodium hydroxide?

6. What compound is responsible for the color observed in C?

7. Write a balanced equation for the reaction in D.

Chapter 43

SUGARS

The isolation of a sugar from a natural source sometimes is a simple matter, as for example the isolation of lactose from milk, for in this case the sugar wanted is not very soluble in water and crystallizes readily. Sometimes it is easier to obtain a derivative of a sugar from a natural source, as for example the isolation of α-methyl D-mannoside by the methanolysis of mannosan (Experiment 43–1).

$$(C_6H_{10}O_5)_n + nCH_3OH \rightarrow nCH_2OH—CH—(CHOH)_3—CH(OCH_3)$$
$$\underset{\qquad\quad O\qquad\quad}{\rule{4cm}{0.4pt}}$$
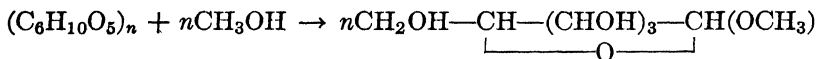
This mannoside crystallizes readily from methanol and thus can be obtained in a pure form. The sugar itself, D-mannose, can be obtained by the hydrolysis of the mannoside in aqueous acid.

$$C_6H_{11}O_5(OCH_3) + H_2O \rightarrow C_6H_{12}O_6 + CH_3OH$$
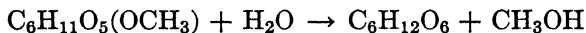
In this way crystalline D-mannose can be obtained, whereas it cannot be crystallized easily by direct hydrolysis of the mannosan, owing to its greater solubility, and thus greater difficulty in crystallizing. In general, sugars are more difficult to obtain crystalline than many of their derivatives. This is due in part to their great solubility in water and in part to the fact that impurities, sometimes even in small amount, make crystallization difficult. Contamination by impurities, such as other sugars or sugar derivatives or inorganic salts, is to be avoided as much as possible. Usually the sugar is obtained in the form of a syrup. Oftentimes it can be made to crystallize by the addition of a suitable organic solvent, as for example alcohol. Sometimes a long period of standing (days or weeks) is necessary. Seeding with a little of the pure substance is highly desirable.

The synthesis of a sugar usually is accomplished by degradation of the next higher sugar or by synthesis from the next lower sugar. Degradation of the next higher sugar produces a single sugar only, whereas

synthesis from the next lower sugar produces two epimeric sugars. Thus isolation of a pure sugar from a reaction product is generally more difficult in the latter case. However, the syntheses are so time-consuming that their value from an instructional point of view in a beginning laboratory course of organic chemistry is hardly commensurate with the time required.

43.11   Glucose Pentaacetates. The preparation of a derivative of a sugar, as for example a glycoside, ether, or ester, is complicated by the fact that there are two series of derivatives, the *alpha* and *beta*. Thus both the sugars themselves and the derivatives exist in two isomeric forms. When in solution it often is possible to cause the isomerization of an *alpha* to a *beta* isomer, or *vice versa*. This change usually is called mutarotation, owing to the fact that the optical rotation of the solution changes during the process. There is a marked difference in the ease with which different substances undergo mutarotation. The sugars themselves are very susceptible to change, mutarotating slowly in pure water and more rapidly in acidic or basic solutions, or in solutions containing anions of weak acids, cations of weak bases, or molecules of undissociated acids. Some derivatives, as for example the hexose pentaacetates, are much more stable and require heating in a solution containing acid or zinc chloride. The systems finally come to equilibrium with both the *alpha* and *beta* isomers present. Also furanose, as well as pyranose isomers are present, usually in much smaller amounts.

The preparation of a pentaacetate of glucose, according to the following equation, is a good example of the importance of the equilibria involved, and of the relative rates of reaction:

$$C_6H_7O(OH)_5 + 5(CH_3CO)_2O \rightarrow C_6H_7O(OCOCH_3)_5 + 5CH_3COOH$$
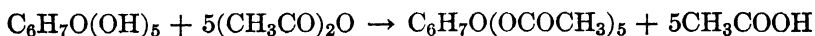
The equilibrium mixture of α-D-glucose and β-D-glucose in aqueous solution at 20° is 36.3% *alpha* and 63.7% *beta* isomer. It probably is not greatly different in other solvents, as for example acetic anhydride. The equilibrium mixture of the *alpha* and *beta* forms of D-glucose pentaacetate in acetic anhydride at 35° is 90% *alpha* and 10% *beta*. Calculation of ΔH from bond energies and resonance energies leads to a value of zero for the energy change between any pair of *alpha* and *beta* isomers. Values determined experimentally are of the order of a few tenths of a kilocalorie. Thus, the equilibria are not markedly affected by changes in temperature.

Different catalysts bring about different results in the acetylation of glucose with acetic anhydride, owing to the fact that they may affect

differently the following possible reactions: (1) the mutarotation involving α-D-glucose and β-D-glucose, (2) the acetylation of α-D-glucose, (3) the acetylation of β-D-glucose, (4) the mutarotation involving pentaacetyl-α-D-glucose and pentaacetyl-β-D-glucose.

With pyridine at 0°, each sugar yields the corresponding pentaacetate, quite pure. The reason is that the sugars themselves do not mutarotate under these conditions. Anhydrous zinc chloride at 0° gives similar results except that some isomerization takes place, because zinc chloride causes some mutarotation of the sugars at 0°. The reactions take place slowly, in 1 or 2 days with pyridine, several days with zinc chloride. The reaction mixtures must be shaken continuously, owing to the low solubility of the sugars in the reaction mixtures.

Sulfuric acid or anhydrous zinc chloride at temperatures near 100° leads to the formation of the *alpha* pentaacetate mainly, whether one starts with α-D-glucose or β-D-glucose. The reason is that each catalyzes the mutarotation of the pentaacetates at 100°, so that the final reaction product is mainly the *alpha* isomer.

Anhydrous sodium acetate at 135° (refluxing temperature) leads mainly to the formation of the *beta* pentaacetate from both α-D-glucose and β-D-glucose. The reason is that it catalyzes the mutarotation of the sugars, it does not catalyze the mutarotation of the pentaacetates, and the rate of acetylation of β-D-glucose exceeds that of α-D-glucose. A large amount of catalyst must be taken, and the mixture heated to boiling for about 1 hour.

43.12 Oxidation of Aldoses. Aldoses can be oxidized to aldonic acids by means of aqueous bromine. Calcium carbonate is added to buffer the solution, since the hydrobromic acid that is formed markedly decreases the rate of oxidation.

$$C_5H_6(OH)_5CHO + Br_2 + H_2O \rightarrow C_5H_6(OH)_5COOH + 2HBr$$

$$3CaCO_3 + 2C_5H_6(OH)_5COOH + 4HBr \rightarrow$$

$$[C_5H_6(OH)_5COO]_2Ca + 2CaBr_2 + 3H_2O + 3CO_2$$
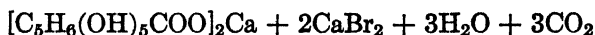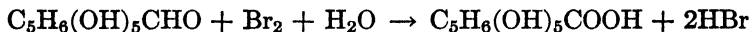
Calcium bromide and a calcium aldonate are the reaction products. The aldonate will not crystallize well from aqueous solution in the presence of calcium bromide. Calcium ion is removed by adding sulfuric acid and filtering. Bromide ion is removed by adding the theoretical amount of silver oxide. Evaporation of the solution at reduced pressure gives the *gamma* lactone of the acid.

Electrolytic oxidation of an aldose in aqueous solution containing a small amount of calcium bromide acts essentially as bromine water does. Bromide ion is oxidized to bromine which is reduced to bromide ion by the sugar. The cycle is repeated until all of the sugar is oxidized. At this point the concentration of bromine increases with resultant coloring of the solution. Since only a small amount of calcium bromide is present, the calcium aldonate will crystallize satisfactorily. Calcium gluconate is prepared in Experiment 43–3 by electrolytic oxidation of D-glucose in the presence of calcium carbonate.

When the current density is about 1 ampere per square decimeter, the current efficiency may be almost 100%. However, if the current density is much higher, the current efficiency drops, owing to the liberation of hydrogen gas at the cathode. The current efficiency does not drop as the current density is decreased, but then a longer time is required. Thus, it is desirable to have more than one check on the course of the reaction, by testing for reducing sugars and by determining the amount of current passed, by coulometer measurements. It is desirable also to calculate the number of ampere-hours as an additional check, but this is only a rough guide, owing to possible variations in the current and to evolution of hydrogen.

Experiment 43–1   Preparation of α-Methyl D-Mannoside and α-D-Mannose

α-METHYL D-MANNOSIDE (Note 1). Add 81 g. (0.5 equiv.) of thoroughly dried finely ground vegetable ivory waste (Note 2) to 100 g. of 85% sulfuric acid in a large mortar of 1- or 2-liter capacity (Note 3) and at such a rate, over a period of $\frac{1}{4}$ to $\frac{1}{2}$ hour, that the temperature will be kept at 30° to 35°. Knead the mass well with a pestle, keep at about 25° for 15 hours (Note 4), and then knead into the mass a mixture of 80 ml. of anhydrous acetone-free methanol and 20 ml. of concentrated c.p. hydrochloric acid. Transfer to a 1- or 2-liter flask, add 500 ml. more of methanol, and reflux on a steam or hot-water bath for 8 hours (Note 5).

Cool somewhat, add about 10 g. of decolorizing carbon, and reflux for another $\frac{1}{2}$ hour. Add 15 or 20 g. of diatomaceous earth (Note 6). Filter rapidly while hot, either through a large fluted filter, or with suction through a hot (Note 7) Buechner funnel. Wash the residue with 40 ml. of hot methanol. In case the liquid is dark colored, add decolorizing carbon, reflux for about $\frac{1}{2}$ hour, and filter as before. Re-

peat, if necessary. Set aside in a cold place for 20 to 50 hours, to crystallize (Note 8).

Collect the solid by suction filtration (test some of the filtrate for reducing sugars with Fehling's solution, Experiment 43–4), wash with 4 or 5 ml. of anhydrous acetone, and dry on porous plate at room temperature. Yield, about 40% of material melting at about 170°, $[\alpha]_D^{20} =$ +78°. Test for reducing action with Fehling's (or Benedict's) solution (Note 9).

Purify by crystallizing from 4 parts of 80% ethyl alcohol. Neutralize carefully with ammonia if the solutions used in crystallization are acidic (Note 10). Test for reducing sugars. Take the melting point and rotation (1% by wt. in water) (Note 11).

D-Mannose from α-Methyl d-Mannoside. Prepare about 400 ml. of a solution of α-methyl d-mannoside in dilute (about 0.5 M) sulfuric acid (Note 12) so that, after hydrolysis, the theoretical concentration of mannose is 10%. Mix thoroughly, and withdraw a 1.0-ml. sample for rotation measurement (Note 13). Heat to about 95°, preferably on a steam or hot-water bath, so as to avoid excessive local overheating (Note 14), until the mannoside is completely hydrolyzed. Avoid loss of solvent. Follow the course of the reaction by removing a 1.0-ml. sample at intervals of about 0.5 hour. Continue until the rotation indicates complete reaction (Note 15).

Neutralize about 90% of the acid, cold, by the slow addition of an aqueous solution of barium hydroxide with thorough mixing (Note 16). Complete the neutralization by heating on a steam or hot-water bath in a large evaporating dish with precipitated barium carbonate, stirring essentially continuously (Note 17). In case the mixture becomes too thick, add more water. After the solution becomes neutral, add some decolorizing carbon if the liquid is colored. Digest warm for some time, filter cold from the insoluble solids (be sure that funnels are thoroughly clean), and extract the filter cake with hot water in a beaker. If the filtrate is colored, heat with decolorizing carbon. Evaporate the filtrates, which should be neutral, clear, and colorless, under reduced pressure with the bath temperature 60° or lower, until the liquid is changed to a thick syrup (Figures 8–4 and 8–5).

While still warm dissolve the syrup in 20 ml. of absolute alcohol, shaking vigorously and warming in a bath at 50°, if necessary, but without needless exposure to water vapor. Reduce again to a thick syrup under reduced pressure as before, and repeat the operation once more (Note 18). Pour the final syrup, which should be colorless, into a conical flask, and wash out the residue by means of five 10-ml. por-

tions of 99.5% acetic acid, shaking well, and warming to 50°. While still warm, add some seed crystals, and stopper well. In case a gum forms on cooling, warm to about 50°, and keep warm until a good crop of crystals forms. Then let cool slowly. Let stand overnight in a cold place or for a few days, in case crystalllization is slow.

Collect the crystalline solid on a small Hirsch or sintered glass funnel, and wash twice with 5 ml. portions of glacial acetic acid and then twice with 5 ml. portions of absolute alcohol. Dry in the air for 1 day and then in an Abderhalden dryer (Figure 5-3C) at 60° under reduced pressure. Take the melting point. Measure the optical rotation on a 4% solution. Calculate the percentage yield (Note 19).

Notes

1. The first step is adapted from *Organic Syntheses*, Collective Vol. I, second edition, p. 371, John Wiley & Sons, 1944; the second step is based on work by Hudson and Jackson, *Jour. Am. Chem. Soc.*, **56**, 958 (1934).

2. Ivory nut waste can be obtained from the Rochester Button Co., Rochester, N. Y. Before use, it should be ground in a mill and sifted through a 20-mesh screen and the fines dried to constant weight at 100°. For the calculation of the number of equivalents, the material is assumed to be a pure polymer of $C_6H_{10}O_5$. If not ground to 20 mesh, it will be necessary to let the paste stand for 2 or 3 days, instead of 15 hours; otherwise, the yield is poor.

3. A crock or enameled kettle could be used.

4. A 60-watt electric lamp suspended about 20 cm. above the mixture is a convenient source of heat.

5. The larger flask is preferred, in case bumping becomes troublesome. Refer to Figure 7-2, and Subsections 7.15 and 7.23.

6. Refer to Subsection 5.25, Filter Aid.

7. Refer to Subsection 5.24, Filtering the Hot Solution.

8. Sometimes crystals form spontaneously in the filter flask, but in general seeding is necessary. The solubility in absolute methyl alcohol at 10° is about 1.5 g. per 100 g. of solvent. In 90% methyl alcohol the solubility is about doubled.

9. This product is pure enough for most purposes, such as the preparation of methyl mannoside tetracetate. Although it is satisfactory for the preparation of α-D-mannose, the control of the hydrolysis reaction is better with the pure product, and crystallization is not so difficult.

10. Hydrolysis of the mannoside is catalyzed by acid.

11. The recovery in this step is 80 to 90% if the mother liquors are worked up (over-all yield, 32 to 38%). The product should melt at 188–189° and have a rotation, $[\alpha]_D^{20} = +79°$ (1% in water). It should not reduce Fehling's or Benedict's solution. The pure compound melts at 193–194°; $[\alpha]_D^{20} = +79.29°$.

12. Subsequent neutralization is much easier if the *exact* amount of acid is known.

13. Dilute the 1.0-ml. sample with a few milliliters of water, and add a few drops of aqueous ammonia to neutralize the acid which otherwise would corrode the polariscopic apparatus. Finally make up to 10.0 ml. Take the rotation of this dilute solution, and record this and subsequent readings in your notebook.

14. The darkening is more pronounced if the acid is more concentrated or if the temperature is higher.

15. The period of half-hydrolysis of α-methyl D-mannoside in 0.5 M hydrochloric acid at 98° is 34 minutes.

16. Do not allow the solution to become alkaline, for the sugar undergoes chemical change then. The required amount of barium hydroxide octahydrate can be weighed out and dissolved in the proper amount of hot water. Because of the low solubility in cold water, 5.6 g. per 100 g. at 15°, the volume of a cold solution might be too large.

17. Manipulation is easier in a wide shallow dish.

18. It is desirable to obtain an anhydrous product since even a slight amount of water renders crystallization difficult and incomplete.

19. Yield is 60% of product having $[\alpha]_D^{20} = +14.8°$ (const.). Pure α-D-mannose melts at 133° and has the following rotations in 4% aqueous solution: Initial, $[\alpha]_D^{20} = +29.3°$; final, $+14.2°$.

Questions

1. What is a mannosan, an araban, a xylan?
2. Do they reduce Fehling's solution?
3. How does ivory nut waste differ chemically from cellulose?
4. Does the purified mannoside reduce Fehling's solution?
5. What is the configuration of α-methyl D-glucoside?
6. What is the structure of β-methyl D-mannoside?
7. What is the configuration of α-methyl D-mannoside?
8. Why should the methanol be acetone-free?
9. What products are formed when α-methyl D-mannoside undergoes hydrolysis?
10. Why is sulfuric acid added in the hydrolysis of α-methyl D-mannoside?
11. Could hydrochloric acid be used instead?
12. What advantage does sulfuric acid have over hydrochloric acid?
13. What is the effect of a hot alkaline solution on D-mannose?
14. Why is not the final precipitation of sulfuric acid done with barium hydroxide?
15. Why is it desirable to remove all water from the syrup?

Experiment 43–2   Preparation of α-D-Glucose Pentaacetate

Weigh 10.0 g. (0.05 mole) of finely divided α-D-glucose monohydrate (Note 1) and 0.35 mole of recently distilled acetic anhydride (Note 2) into a 200- or 400-ml. round-bottomed flask. Place a thermometer in the flask (Note 3). Add 1 drop of concentrated sulfuric acid (Notes 4 and 5) from a medicine dropper, at once mix the contents with a swirling motion, and continue the swirling until the solid has disappeared. The reaction should start immediately as evidenced by increase in temperature and diminution in the amount of solid. If it does not, bring the temperature to 50° or 60° by immersing in warm water (Notes 6 and 7). Should the liquid begin to boil, cool slightly by dipping the flask momentarily in cold water (Note 8). After about 80% of the solid has dissolved and the reaction has slackened, usually in about

¼ hour, add 4 or 5 more drops of sulfuric acid. Break up any crystals by means of a footed stirring rod. After all the sugar has dissolved, heat on a steam bath for 0.5 to 1 hour.

Pour the still warm (not hot) reaction solution slowly in a *very* thin stream into three to five times the volume of *cold* water (or water and ice), under *vigorous* agitation. Continue stirring, preferably with a stirring rod, so as to stir the organic phase well, until it becomes crystalline. From time to time break up the aggregates of solid with a footed stirring rod, or better yet grind in a mortar, so that finally all particles are fine, in order to facilitate extraction of the acid by water. As soon as the product is *completely* crystalline, collect by suction filtration, and wash with small portions of cold water. Allow to dry completely in the air (Note 9).

Crystallize from the minimum quantity of hot ethyl alcohol (about 10 g. per gram; refer to Question 12), adding decolorizing carbon if the solution is colored. As the hot filtrate cools, induce crystallization by scratching, and, also, preferably, by seeding. Cool to *ca.* 0°, and let stand cold for some time, stirring frequently to promote crystallization. Collect by suction filtration, and wash with cold alcohol. Collect the filtrate separately, and let it stand in the cold room for a few days to obtain a possible second crop. Keep this separate. After each crop is thoroughly dry, take the melting point and optical rotation. If not pure, recrystallize. Calculate the percentage yield (Note 10). Calculate the purity from the rotation.

Notes

1. Ordinary commercial crystalline glucose (corn sugar) is α-D-glucose monohydrate. Anhydrous glucose likewise is satisfactory. In this case, for 0.05 mole of anhydrous sugar take 0.3 mole of acetic anhydride.

2. Or an equivalent amount of technical acetic anhydride (approximately 92%). However, since acetic anhydride deteriorates in glass-stoppered vessels, owing to access of moisture, generally it is unwise to use any but freshly distilled material.

3. Leave the thermometer in the mixture until the reaction slackens.

4. Sulfuric acid is a powerful catalyst for the reaction of acetic anhydride with alcohols. If more is added the reaction may proceed too rapidly and get out of control.

5. To prepare the *beta* isomer, replace the sulfuric acid with 0.02 mole of *freshly fused* anhydrous sodium acetate. Heat slowly to refluxing temperature, agitating frequently. After refluxing gently for 1 hour, pour into cold water, as previously. Rubber stoppers are disintegrated by hot acetic acid.

6. Needless access of water vapor should be avoided.

7. This is not necessary when working with larger amounts of materials, for then the temperature rises rather rapidly.

8. Some darkening may take place at temperatures above 100°.

9. The yield of crude product is about 90%. This fuses at a much lower temperature than does the pure α-acetate. On this account it should be dried at room temperature.

10. Physical constants of the pure pentaacetates: *alpha* form, m.p., 114°; $[\alpha]_D^{20}$, +101.6° in 5% $CHCl_3$ solution; solubility in H_2O at 18°, 0.15; solubility in 95% C_2H_5OH at 15°, 1.9; *beta* form, m.p., 135°; $[\alpha]_D^{20}$, +3.8 in 7% $CHCl_3$ solution; solubility in H_2O at 18°, 0.1; solubility in 95% C_2H_5OH at 15°, 1.3 g. per 100 g. Yield of purified product: *alpha*, 45%; *beta*, 55%.

Questions

1. Explain the existence of the *alpha* and *beta* forms of D-glucose and of D-glucose pentaacetate.

2. Explain why the pentaacetates do not isomerize as easily as the two forms of the sugar.

3. What is meant by the word furanose? pyranose?

4. What is meant by aldehydo-D-glucose?

5. How do aldehydo-D-glucose and aldehydo-D-mannose differ in configuration?

6. What other names are used for D-glucose?

7. What substances can be used to catalyze the acetylation of D-glucose?

8. Would you say that sulfuric acid is a weak or powerful catalyst for the acetylation?

9. Which form of D-glucose is acetylated the more rapidly: the *alpha* or the *beta* form?

10. Explain why the *alpha* isomer is the main product with sulfuric acid as the catalyst, and the *beta* with sodium acetate.

11. Why does the crude product fuse at a relatively low temperature?

12. What weight of alcohol is needed to hold the other isomer (the impurity) in solution at 15°, if it is assumed that the equilibrium that exists at 35° exists also at other temperatures?

13. What weight of the desired isomer will be lost at the same time?

Experiment 43–3   Preparation of Calcium Gluconate

Equip a 2-liter three-necked flask in which all three necks are vertical with a mechanical stirrer and two graphite electrodes 22 mm. in diameter and sufficiently long to reach to the bottom of the flask (Note 1). Place in the flask 0.25 mole of anhydrous D-glucose or an equivalent amount of the monohydrate (Note 2), 0.04 mole of calcium bromide or of bromine, about 0.5 mole of precipitated calcium carbonate (Note 3), and 1 liter of water. In place of pure water and calcium bromide, use if available the solution left over from a recent previous experiment, and dilute to 1 liter. Attach in series an ammeter, a rheostat, and a reversing switch, so that the electrodes may be reversed from time to time, to equalize the decrease in size, for sometimes the electrodes dis-

integrate slowly, or become coated with a deposit. It is desirable but not necessary to place a coulometer in series, for accurate determination of the amount of current passed (Note 5). Calculate the amperage which will give a current density of 1.0 to 1.5 amperes per square decimeter, as this has been found to be about the maximum that is economical of current. Adjust resistance and voltage so as to secure this amperage. Usually 12 volts is a sufficiently high voltage, even when the electrodes are well separated (Note 6).

Stir the solution while the current is passing, and apply cooling (Note 7). If the current density becomes too large, owing to an increase in the amount of electrolyte, increase the resistance, reduce the voltage, and/or move the electrodes further apart. Hydrogen and carbon dioxide are evolved. The solution should be only slightly acidic. No color of bromine should be apparent until the oxidation is nearly completed. After oxidation is about 80% completed (Note 8), follow the course of the reaction by removing small samples at intervals and testing for reducing sugars with Fehling's solution or Benedict's solution (Note 9). Stop when the tests are negative or when 96% of the sugar has been oxidized (Note 10). Keep a neat complete record of voltage, amperage, and temperature, and also of the tests for reducing sugar.

Obtain a clear filtrate by suction filtration at about 50° through clean apparatus. Remove water by distillation at reduced pressure with heating bath at 60° or below (refer to Chapter 8, especially Subsection 8.24). Continue until the volume is about 150 ml. or until the liquid is a thin syrup (Note 11). Transfer while still warm to a beaker, and wash out the flask with a small amount of hot water.

To facilitate crystallization add to a small portion (5 ml.) of the liquid an equal volume of alcohol, a little at a time, with good mixing. This decreases the solubility of the calcium gluconate and at the same time reduces the viscosity, thus making crystallization easier. Induce crystallization by scratching, or by seeding, and stir frequently. Crystallization is slow. When a good crop has formed, transfer the mixture to the main solution for seeding (Note 12). Mix thoroughly, stir at intervals, and let stand overnight or longer. Collect the solid by suction filtration, and press out the solid so long as any liquid is obtainable. Wash once with 25 or 30 ml. of water by transferring the filter cake to a beaker and stirring thoroughly. Filter as before (Note 13). Finally remove residual liquid by strong pressure between absorbent paper, and let the solid dry completely in the air over a period of days. Calculate the percentage yield (Note 14) and the current efficiency (Note 15).

Notes

1. A more convenient arrangement is shown in Figure 43–1. This is a 2-liter vessel A (beaker or jar) with a wooden top which has openings for a mechanical stirrer B, the four carbon electrodes C, and two cold-finger condensers D. Each electrode can be moved horizontally about ½ inch, and thus the distance between them can be varied from ¾ to 1¾ inch. The condensers are located close to the electrodes, where most of the reaction takes place.

2. Ordinary commercial crystalline glucose (corn sugar, dextrose) is α-D-glucose monohydrate.

3. See 43.12 regarding value of calcium bromide and calcium carbonate.

4. It is a great saving of time to have available a board on which are mounted voltmeter, ammeter, rheostat, and reversing switch.

5. The coulometer is desirable for calculating the current efficiency.

6. This is a higher potential than is required theoretically for the oxidation due largely to resistance in the electrodes and in the solution.

7. The yield decreases if the temperature rises.

8. Theoretically 0.5 Faraday (13.4 ampere-hours) is required for the oxidation of 0.25 mole of D-glucose to D-gluconic acid.

9. Refer to Experiment 43–4B in regard to making the test.

10. The solubility of calcium gluconate is increased by dissolved sugar.

11. Calcium gluconate is slightly soluble in water at 18°, 3.5 g. of anhydrous salt per 100 g., and is soluble in hot water. However, it easily forms supersaturated solutions which contain much

Top view

FIG. 43–1 Apparatus for Electrolytic Oxidation of D-Glucose

more of the solid, and these are slow to crystallize, especially if the viscosity is high. If preferred, the distillation can be continued until solid separates on the upper part of the flask, but there is no great advantage in concentrating the solution so far. If desired, the main filtrate can be concentrated and a small second crop obtained. However, the dissolved calcium bromide increases the solubility of calcium gluconate. A better recovery of the dissolved calcium gluconate is possible if calcium bromide is removed by means of silver oxalate.

12. If desired, alcohol may be added to the main portion also, in small portions, until the precipitate formed dissolves only slowly on mixing. Then the seed crystals are added.

13. The combined filtrates may be used for oxidation of a second portion of D-glucose. Naturally, the yield this time should be nearly quantitative, since there is a quantity of glucose and gluconic acid already present that is equal to the amount lost in the oxidation and in the final recovery. No additional bromide is added. This mother liquor is better to use for a second preparation than pure water, but unless it is to be utilized soon it should be discarded, since it is attacked by microorganisms.

14. The hydrated form on exposure to air slowly effloresces to the anhydrous form, which has specific rotation, $[\alpha]_D^{20} = +5.8$ to $+5.94$ (in 2% solution). The yield is 75 to 78%.

15. These directions are adapted from work of Isbell, Frush and Bates, *Ind. Eng. Chem.*, **24**, 375 (1930); *Bureau of Standards Jour. of Res.*, **8**, 571 (1932).

Questions

1. What is the theoretical amount of calcium carbonate required?
2. Why is an excess desirable?
3. How does an increase in the amount of electrolyte cause the current density to become larger?
4. What causes an increase in the amount of electrolyte?
5. Show how to calculate the number of ampere-hours required for the oxidation. One Faraday is 96,500 coulombs.
6. Is there a discrepancy between the actual and theoretical amount of electricity required?
7. Explain how hydrogen and carbon dioxide are evolved.
8. At which electrode is hydrogen evolved?
9. Why is not carbon dioxide evolved mainly at an electrode?
10. Why is the solution acidic?
11. Why is it only slightly rather than strongly acidic?
12. What is the formula of calcium D-gluconate? of D-glucono-γ-lactone?
13. How may the latter be obtained from the former?
14. What are the main impurities in the final product?
15. What steps would you recommend for their removal?

Experiment 43–4   Properties of Carbohydrates

A CARBOHYDRATES IN GENERAL. *Molische test* (modified by Mulliken). To a very small amount of a carbohydrate (D-glucose, sucrose, starch, filter paper) in a test tube, add 2 drops of a 10% solution of α-naphthol in chloroform (or the equivalent). Pour 2 ml. of concentrated sulfuric acid carefully into the test tube inclined at an angle, so that it forms a distinct lower layer. A purple–red zone should form in a few seconds. On the addition of 4 or 5 ml. of water, after standing for a few minutes, a purple precipitate forms (Note 1). Repeat, using furfural in place of carbohydrate.

B MONOSACCHARIDES. *1. Effect of alkali on monosaccharides.* To
0.1 to 0.2 g. of a monosaccharide in 5 or 10 ml. of water, add 1 or 2 ml.
of sodium hydroxide solution, and heat to boiling. Recall the behavior
of acetaldehyde under these conditions (Experiment 25–5B).

2. Test for reducing sugars. Reduction of Fehling's solution. Place
0.05- to 0.1-g. portions (Note 2) of D-glucose, D-fructose, D-mannose,
D-galactose in test tubes, and add 10 ml. of Fehling's solution (5 ml. each
of I and II; Note 3) and 10 ml. of water. Mix thoroughly, and place
in a boiling water bath for 5 minutes or until the precipitate becomes
red. At the end of this time, carefully pour off the liquid. Note any
residue. The color is brought out by adding water.

3. Reduction of Benedict's solution. Repeat test 2, but use Benedict's
solution (Note 4).

4. Silver mirror by reduction of silver ion (Note 5). In a clean test
tube prepare some ammoniacal silver nitrate, add to it a dilute solution
of D-glucose, and set aside. Repeat, but add 1 or 2 drops of sodium
hydroxide solution before adding the sugar solution (Note 6).

5. Hydrazone and osazone formation. To 0.5 g. (about 0.003 mole)
of D-glucose, D-fructose, D-mannose, and D-galactose in each of four wide
test tubes add 1.5 g. (about 0.01 mole) of sodium acetate trihydrate.
Make a solution of phenylhydrazine hydrochloride (colorless or only
slightly colored; Note 7) by pouring 75 ml. of hot water, about 85°,
onto 10 g. of the solid. If the solution is cloudy, filter rapidly through
a fluted filter paper. Add 15 ml. of the still hot solution (0.014 mole)
to each of the four test tubes, agitate until the contents are homogene-
ous, and immerse in a bath of boiling water. Note the time at which
precipitation starts (Note 8) and the color of the precipitate.

C DISACCHARIDES. *1. Effect of alkali on disaccharides.* Repeat B,
1, with sucrose and maltose instead of a monosaccharide.

2. Sucrose and calcium hydroxide. Shake 10 ml. of a rather concen-
trated solution of sucrose (20 to 25%) with an excess of milk of lime,
which you have prepared by slaking some good quicklime and then
shaking with enough water to make a workable paste. After shaking
with the sugar solution for about 5 minutes, let a part of the mixture
stand and heat another part in boiling water (Note 9).

3. Reducing action of disaccharides. Dissolve 0.2 g. each of sucrose
and maltose in 20 ml. of water. Divide each into two parts. Test one
half for reducing action with either Fehling's or Benedict's solution B,
2 or B, *3*.

4. Invert sugar. To the other half of the sucrose solution, add 1 ml.
of concentrated hydrochloric acid, boil for 1 minute, cool, and neutralize
with sodium hydroxide. Make slightly acidic, rather than basic. Test

for reducing sugars according to B, *2* or B, *3*; also test with ammoniacal silver nitrate (Note 10).

Notes

1. Sulfuric acid converts pentoses and pentosans to furfural, hexoses and hexosans to α-hydroxymethyl–furfural. These then react with the naphthol to give the color test.

2. If the amount of sugar is too great, the precipitate of cuprous oxide does not have the characteristic red color.

3. Fehling's solution I is a solution of copper sulfate pentahydrate, 73.278 g. per liter; solution II is a solution of Rochelle salt 345 g. and sodium hydroxide 250 g. per liter. The precipitate of yellow cuprous hydroxide slowly changes when heated to red cuprous oxide. In the volumetric method of analysis, 1 ml. of mixed I and II (0.50 ml. of each), when diluted to 5 ml., is equivalent to 4.8 mg. of anhydrous D-glucose.

4. In Benedict's solution, 17.3 g. of copper sulfate, 173.0 g. of sodium citrate, and 100.0 g. of sodium carbonate are dissolved in 1 liter. Benedict's solution is more sensitive since it does not contain a strong base as does Fehling's solution. Sodium hydroxide itself causes the monosaccharide to decompose.

5. For obtaining a mirror, the glass must be clean (a slight trace of stannous chloride is claimed to be an advantage) and free of any oil film; the concentration of reactants should not be high, and the reaction should take place slowly. Increase in alkalinity gives a faster reaction.

6. The ammoniacal silver nitrate solution is called Tollen's reagent when sodium hydroxide has been added. The solutions should never be allowed to stand around, for a dangerously explosive substance is formed.

7. Phenylhydrazine hydrochloride is preferred over phenylhydrazine because it is more stable and more convenient to use. It decomposes slowly, however. In case it is dark colored, take more than 10 g. (about 12 g.).

8. An aid in the identification of a sugar is the time necessary for the formation of the slightly soluble hydrazone or osazone. The appearance of the recrystallized solid is also useful. Mannose phenylhydrazone is only slightly soluble in hot water, whereas the hydrazones of the other sugars are quite soluble.

9. Recovery of sucrose from molasses depends on this or a similar change.

10. Sucrose can be determined quantitatively by means of the inversion process, by the use of either reducing methods or polarimetric methods. For purposes of analysis, inversion is usually carried out at 68–69°, over a period of 10 minutes, as under such conditions there is less decomposition of the sugar.

Questions

1. What is meant by the expression aldose? ketose?

2. State if the sugars used are aldoses or ketoses.

3. What is meant by the expression, reducing sugar? Are D-glucose, D-fructose, and D-mannose reducing sugars?

4. How would hydroxymethyl–furfural be formed in test A?

5. Write an equation showing the formation of metallic silver by the use of D-glucose.

6. Write the equation for the reaction of phenylhydrazine with D-glucose, D-fructose, D-mannose. How do you account for any difference in color?

7. Is this reaction of value in distinguishing these three sugars from each other? Explain.

8. What is meant by hydrazone? osazone?

9. Why do the osazones of glucose and fructose form at different rates but have the same crystal form?

10. What conclusions can you draw from the action of alkali on sucrose and maltose?

11. Explain what happens in test C, *2*.

12. What application is made of this reaction in industry?

13. What is meant by inversion?

14. How do sucrose and maltose differ in behavior towards Fehling's or Benedict's solution? What does this indicate in regard to structure?

15. How many osazones are formed from invert sugar and phenylhydrazine? Explain.

PYRROLES

The pyrroles constitute one of the most important classes of nitrogen-containing heterocyclic compounds. They are very widely distributed in nature and occur in such very important compounds as the porphyrins, among which are chlorophyll and haemoglobin.

Pyrrole and β-substituted pyrroles may be synthesized by (a) the reduction of succinimide and substituted succinimides. Pyrrole and homologs may be synthesized by (b) cyclization of 1,4-dioxo compounds with ammonia or primary amines and (c) the condensation of α-amino-ketones with other ketones. Pyrrole itself can be prepared readily by (d) the decomposition of ammonium mucate or ammonium saccharate.

(a)

$$
\begin{array}{c}
\text{H} \\
| \\
\text{N} \\
\text{OC} \quad \text{CO} \\
| \qquad | \\
\text{H}_2\text{C}\text{———}\text{CH}_2
\end{array}
+ 2\text{Zn} \rightarrow
\begin{array}{c}
\text{H} \\
| \\
\text{N} \\
\text{HC} \quad \text{CH} \\
\| \qquad \| \\
\text{HC}\text{———}\text{CH}
\end{array}
+ 2\text{ZnO}
$$

$$
\begin{array}{c}
\text{H} \\
| \\
\text{N} \\
\text{O}=\text{C} \quad \text{C}=\text{O} \\
| \qquad | \\
\text{RHC}\text{———}\text{CHR}
\end{array}
+ 2\text{Zn} \rightarrow
\begin{array}{c}
\text{H} \\
| \\
\text{N} \\
\text{H}-\text{C} \quad \text{C}-\text{H} \\
\| \qquad \| \\
\text{R}-\text{C}\text{———}\text{C}-\text{R}
\end{array}
+ 2\text{ZnO}
$$

(b)

$$
\begin{array}{c}
\text{O} \quad \text{O} \\
\text{HC} \quad \text{CH} \\
| \qquad | \\
\text{H}_2\text{C}\text{———}\text{CH}_2
\end{array}
+ \text{NH}_3 \rightarrow
\begin{array}{c}
\text{H} \\
| \\
\text{N} \\
\text{HC} \quad \text{CH} \\
\| \qquad \| \\
\text{HC}\text{———}\text{CH}
\end{array}
+ 2\text{H}_2\text{O}
$$

$$
\begin{array}{c}
\text{O} \quad \text{O} \\
\text{R}-\text{C} \quad \text{C}-\text{R} \\
| \qquad | \\
\text{R}'\text{HC}\text{———}\text{CHR}'
\end{array}
+ \text{NH}_2\text{R}'' \rightarrow
\begin{array}{c}
\text{R}'' \\
| \\
\text{N} \\
\text{R}-\text{C} \quad \text{C}-\text{R} \\
\| \qquad \| \\
\text{R}'-\text{C}\text{———}\text{C}-\text{R}'
\end{array}
+ 2\text{H}_2\text{O}
$$

(c)

$$CH_3C\!\!\diagup\!\!^O\ CH_3 + \ ^{NH_2}\!\!\diagdown CHR\ O\!\!=\!\!CCH_3 \rightarrow CH_3C\!\!\diagup\!\!^{NH}\!\!\diagdown CR\ HC\!\!-\!\!CCH_3 + 2H_2O$$

(d)

$$NH_4^+ + \bar{O}\!\!-\!\!C\!\!\diagdown^{O\ H}\!\!\diagup O\quad O\!\!\diagdown^{H\ O}\!\!\diagup C\!\!-\!\!\bar{O} + NH_4^+$$
$$HC\qquad CH$$
$$HC\!\!-\!\!CH$$
$$HO\qquad OH$$
$$\rightarrow$$

$$\overset{H}{\underset{N}{|}}$$
$$HC\diagup\ \diagdown CH$$
$$HC\!\!-\!\!CH + NH_3 + 4H_2O + 2CO_2$$
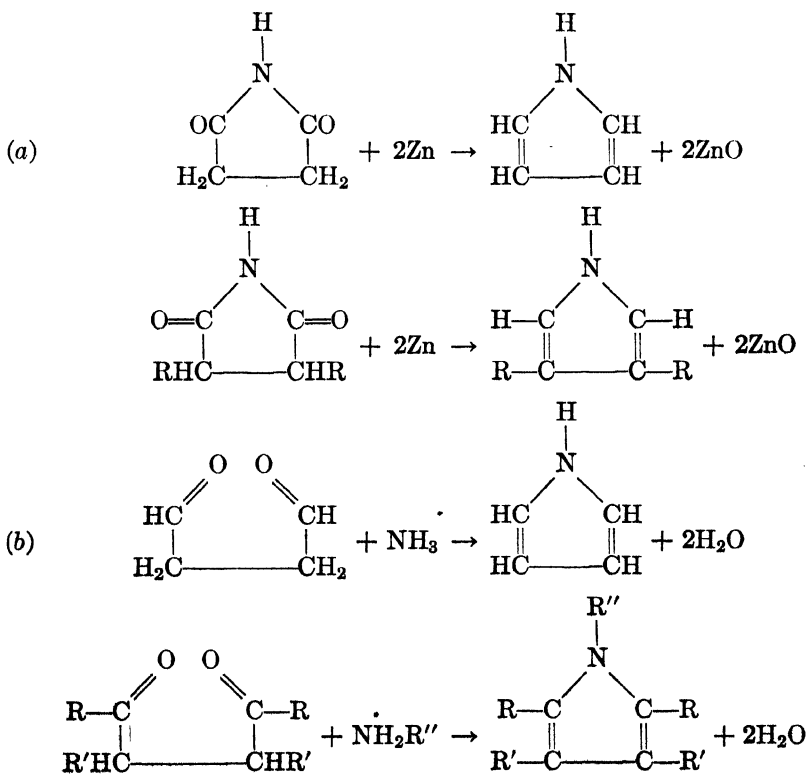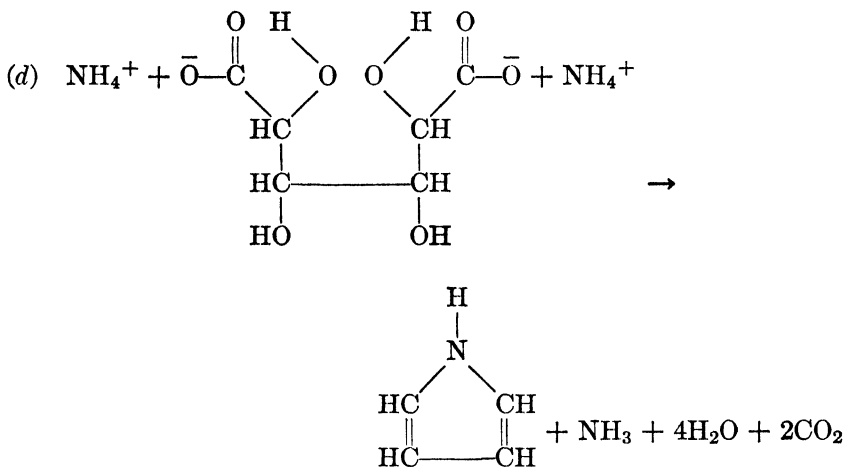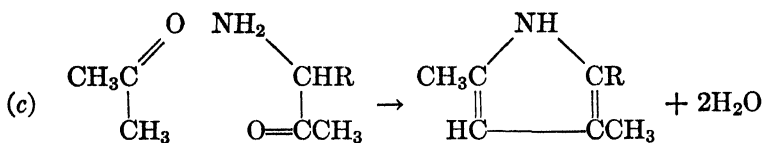
44.11 Reduction of Succinimides. In method a, reaction can be brought about by heating the compound with sodium metal, with zinc dust alone, or with zinc dust and acetic acid. This process can be used to yield homologs with a substituent in one or both of the *beta* positions, starting with imides with a substituent in one or both of the *alpha* positions.

44.12 Condensation of 1,4-Dioxo Compounds with Ammonia. In method b, reaction is brought about usually by heating an alcoholic solution of ammonia with the dioxo compound to about 150° in a sealed tube for about 1 hour. In some cases in which reaction takes place readily, as for example with ethyl diacetylsuccinate (Experiment 44–1), the reaction takes place with ammonium acetate in boiling glacial acetic acid. Ammonia may be replaced by a primary amine to yield the corresponding N-substituted pyrrole. Thus, by the use of properly substituted ketones and/or monosubstituted ammonias, pyrroles with a substituent in any or in all positions may be obtained. This is a very convenient synthesis, since a large variety of 1,4-diketones are available from the acetoacetic ester synthesis (Chapter 40). Thus α,α'-dimethyl-β,β'-dicarbethoxy pyrrole can be converted into α,α'-dimethyl pyrrole by heating with potassium hydroxide, which effects saponification of the ester and decarboxylation of the resulting salt, all in one operation.

$$
\text{NH}_3 + \quad
\begin{array}{c}
\text{CH}_3\text{C}{=}\text{O} \quad \text{O}{=}\text{CCH}_3 \\
| \qquad\qquad | \\
\text{EtOCOCH}\text{------}\text{CHCOOEt}
\end{array}
\quad \rightarrow
$$

ethyl α,α′-diacetylsuccinate

$$
\begin{array}{c}
\text{H} \\
| \\
\text{N} \\
\text{CH}_3\text{---C} \qquad \text{C---CH}_3 \\
\| \qquad\qquad \| \\
\text{EtOCO---C}\text{------}\text{C---COOEt}
\end{array}
\quad + 2\text{H}_2\text{O}
$$

α,α′-dimethyl-β,β′-dicarbethoxy pyrrole

$$
2\text{KOH} +
\begin{array}{c}
\text{H} \\
| \\
\text{N} \\
\text{H}_3\text{C---C} \qquad \text{C---CH}_3 \\
\| \qquad\qquad \| \\
\text{EtOCO---C}\text{------}\text{C---COOEt}
\end{array}
\quad \rightarrow
$$

$$
\begin{array}{c}
\text{H} \\
| \\
\text{N} \\
\text{H}_3\text{C---C} \qquad \text{C---CH}_3 \\
\| \qquad\qquad \| \\
\text{KOCO---C}\text{------}\text{C---COOK}
\end{array}
\quad + 2\text{EtOH}
$$

$$
2\text{KOH} +
\begin{array}{c}
\text{H} \\
| \\
\text{N} \\
\text{H}_3\text{C---C} \qquad \text{C---CH}_3 \\
\| \qquad\qquad \| \\
\text{KOCO---C}\text{------}\text{C---COOK}
\end{array}
\quad \rightarrow
$$

$$
\begin{array}{c}
\text{H} \\
| \\
\text{N} \\
\text{H}_3\text{C---C} \qquad \text{C---CH}_3 \\
\| \qquad\qquad \| \\
\text{HC}\text{------}\text{CH}
\end{array}
\quad + 2\text{K}_2\text{CO}_3
$$
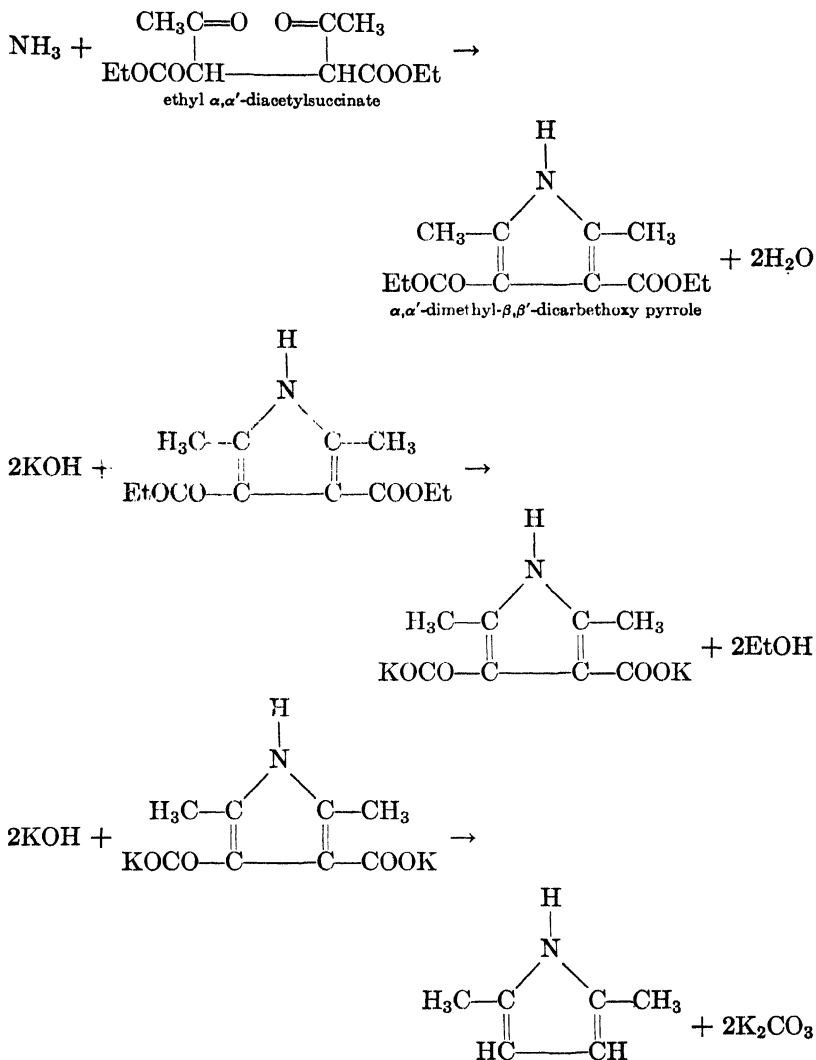
44.13   Condensation of Ketones with Amino Ketones. Method *c* is very useful since pyrroles with substituents in any position can be obtained by the proper selection of the ketone and aminoketone. Since aminoketones are not stable and undergo intermolecular condensation, they are prepared as intermediates by the reduction of the proper nitrosoketones with zinc and acetic acid. The nitrosoketone is prepared by the action of butyl (or amyl) nitrite on the ketone.

$$CH_3-\overset{\overset{\displaystyle O}{\|}}{C}-CH_2-CH_3 + C_4H_9-O-N=O \rightarrow$$

$$CH_3-\overset{\overset{\displaystyle O}{\|}}{C}-CH(NO)-CH_3 + C_4H_9OH$$

$$CH_3-\overset{\overset{\displaystyle O}{\|}}{C}-CH(NO)-CH_3 + 2Zn + 4CH_3COOH \rightarrow$$

$$CH_3-\overset{\overset{\displaystyle O}{\|}}{C}-CH(NH_2)-CH_3 + 2(CH_3COO)_2Zn + H_2O$$
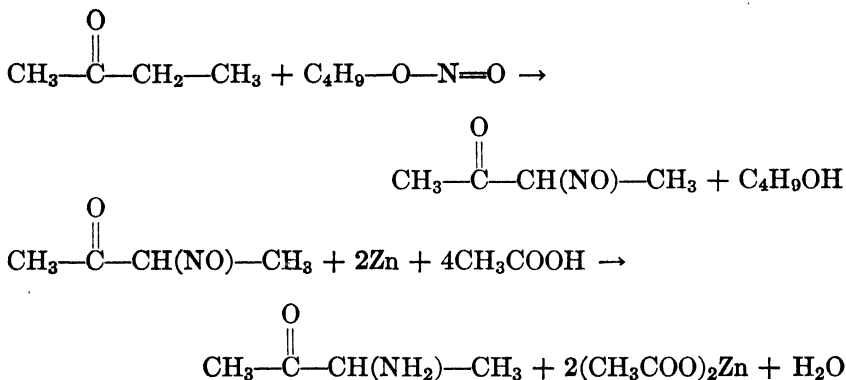
The second ketone is then coupled with the aminoketone without separating the latter from the reaction mixture. The second ketone is added, and condensation takes place when the mixture is made alkaline. The yields in this reaction are greatly increased if β-diketones are used or still better if β-keto esters are used. When unsymmetrical ketones are used, mixtures result.

44.14 Pyrolysis of Ammonium Saccharate or Ammonium Mucate. Method d is limited to the preparation of the unsubstituted pyrrole. The reaction is best carried out by the use of glycerol as a solvent. Replacing ammonia by a primary amine leads to the formation of N-substituted pyrroles.

44.15 Indigo Synthesis. In the synthesis of indigo (Experiment 44–2) ring closure takes place when the potassium salt of N-phenylglycine is fused with potassium hydroxide. The product is the potassium salt of indoxyl.

anion of N-phenylglycine   anion of indoxyl
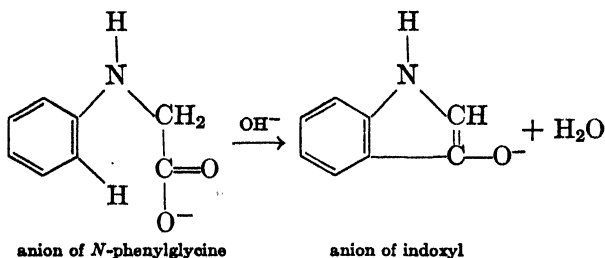
A similar condensation was brought about in the preparation of β-chloroanthraquinone (Experiment 38–3) by sulfuric acid. The presence of acid is not desirable in this condensation, however, since phenylglycine undergoes scission when heated with concentrated sulfuric acid. Also, the yield of indoxyl is low when potassium hydroxide is the reagent,

because at the high temperature required the water formed causes hydrolytic scission.

$$C_6H_5NHCH_2COOK + HOH \rightarrow C_6H_5NH_2 + CH_2OHCOOK$$
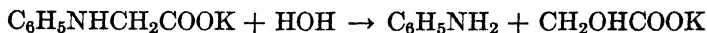
However, by the addition of sodamide to the alkali, the condensation reaction takes place at a lower temperature, namely, 240° to 250°, and, more, important, sodamide reacts with water and thus minimizes the scission reaction.

$$HOH + NaNH_2 \rightarrow NaOH + NH_3$$
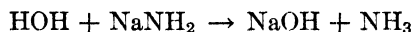
On the addition of water at room temperature a sodium or potassium salt of indoxyl undergoes hydrolysis, and indoxyl is formed.
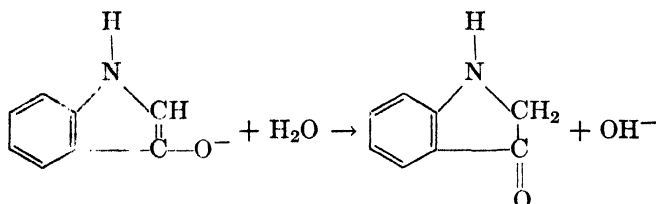
Oxygen oxidizes indoxyl to indigo.

indoxyl   indigo
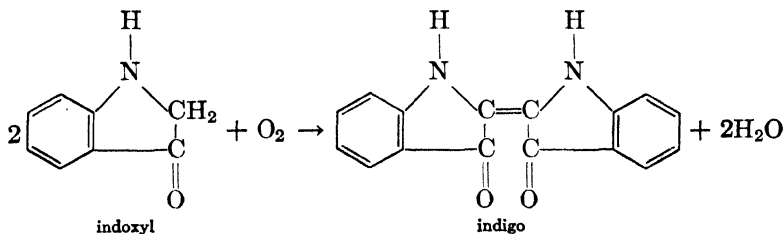
Experiment 44–1   Preparation of α,α'-Dimethylpyrrole

CYCLIZATION. Dissolve 0.1 mole of ethyl diacetylsuccinate (Experiment 40–3) in a small amount of hot glacial acetic acid. Add a 200% excess of ammonium acetate, and reflux for 10 to 20 minutes. Cool, and add water until no more α,α'-dimethyl-β,β'-dicarbethoxypyrrole separates. Crystallize from either aqueous acetic acid or aqueous alcohol. Calculate the percentage yield for this condensation step (Note 1).

SAPONIFICATION AND DECARBOXYLATION. In a distilling flask with a low side arm (Note 2) place an amount of solid potassium hydroxide (Note 3) such that there will still be some unreacted base after all reactions have taken place (Note 4). Add an amount of diethylene

glycol (Note 5) such that the resulting solution will be about 2 M, and heat to about 100°, agitating until the solid has largely dissolved. Cool somewhat, add the α,α'-dimethyl-β,β'-dicarbethoxypyrrole, attach a small condenser, and heat cautiously with a *small* flame so as to distil *slowly* a mixture of ethyl alcohol, water, and α,α'-dimethylpyrrole. Continue as long as a reaction product is being obtained, and stop when it is evident that the distillate is largely diethyleneglycol, as shown by the distilling temperature and the viscous nature of the cold distillate.

Add water to the distillate until the volume of the aqueous phase is three to five times that of the organic phase. In case the latter is very small, or nonexistent, return the diluted distillate to the flask, and repeat the distillation, but more slowly. Add some potassium carbonate or other suitable inorganic salt to decrease the solubility of the pyrrole in the aqueous alcoholic phase. Draw off the latter. Repeat until alcohol and glycol are well removed. If desired, ethyl ether may be added, to minimize loss in handling. Dry the organic phase with a little solid caustic.

Distil slowly. Heat with a small flame, and collect the product in a 5° range near the boiling point of α,α'-dimethylpyrrole (Note 6). Calculate the yield from ethyl diacetylsuccinate (Note 7).

Notes

1. The pure compound melts at 99°. The melting point of the solid is greatly affected by impurities. On this account the use of a mixed solvent is less desirable than a single solvent. Yield at this step, 85%.

2. Because of the rather high boiling point a low side arm is preferred.

3. The flake product dissolves more rapidly than the pellet or stick form. Complete solution of the solid is not necessary. A technical grade is satisfactory.

4. Although in general decarboxylation of acids proceeds more readily than that of salts, acid conditions are not satisfactory here since pyrroles decompose (polymerize) under acid conditions. Decarboxylation proceeds more readily if excess base is present. Consult instructor if uncertain about the amount of base required.

5. This solvent is selected because of its high boiling point, namely, 245°.

6. Boiling point, 169°.

7. Yield is 70%.

Questions

1. Is pyrrole an aromatic compound?
2. What type of cyclic compound is pyrrole?
3. Is pyrrole acidic or basic?
4. Is pyrrole stable in contact with acids or bases?
5. How many dimethylpyrroles are possible?
6. What is meant by decarboxylation?

7. Which type of pyrrole carboxylic acid undergoes decarboxylation the more readily?

8. Why is the high boiling point of diethyleneglycol a desirable property?

9. How does ethyl alcohol happen to be in the distillate?

10. By what other reaction may α,α'-dimethylpyrrole be synthesized?

Experiment 44–2   Preparation of Indigo

POTASSIUM PHENYLGLYCINATE.   To 0.05 mole of N-phenylglycine add a 5% excess of potassium hydroxide dissolved in a minimum volume of hot water.   Mix thoroughly.   Evaporate to complete dryness at temperatures under 120°, and thoroughly dry the residue by heating for 2 or 3 hours in an oven at 120° (Note 1).   Two or three times during this period grind the product to a fine powder, and put back for additional drying.   The solid finally should be a fine dry powder.

SODAMIDE.   Attach a Dry Ice reflux condenser (Figure 7–2, I) to a two-necked flask (0.5 or 1 liter) by means of a tight connection, so that water cannot leak through (Note 2).   To the outlet tube of the condenser attach a guard tube of soda lime or of solid caustic (Note 3).   Attach a glass inlet tube to the other neck, and connect this to a tank of ammonia (*Hood*).   After the condenser is charged with Dry Ice and isopropyl ether (Note 4), collect liquid ammonia by allowing gaseous ammonia to enter as rapidly as the condenser can condense it, or run in liquid ammonia by placing the tank in the proper position (usually horizontal) and opening the valve wide.   Keep the condenser charged with Dry Ice, and collect 100 to 200 ml. of liquid ammonia.   Close the second neck.   Let the flask stand for a while so that it will be coated with an insulating layer of ice.   Make a note of the rate of reflux, as an aid to judging, later, when the reaction between metallic sodium and ammonia is completed.

From a larger piece of metallic sodium trim off the crust (*Caution:* Note 5), and cut off a piece approximately 0.2 g. at. wt. of sodium. Without delay add the sodium, in as large pieces as possible to the flask, and follow this with about 0.1 g. of anhydrous ferric chloride (Note 6).   The liquid boils vigorously, owing to the heat of the reaction and to the evolution of hydrogen gas.   For a time the refluxing of liquid ammonia is much more rapid than formerly.   As the reaction proceeds, this gradually lessens, and the intense blue color gradually changes to brown or red, because of iron (Note 7).   Unreacted sodium is undesirable because then the yield of indigo is much less.   The time required varies from 0.5 to 2 hours.   After the metallic sodium has reacted, allow about 100 ml. of light petroleum ether (40–60°) to flow slowly into the

flask from a dropping funnel attached to the second neck. Remove the reflux condenser, attach the guard tube (Note 8), and allow the ammonia to evaporate. The sodamide is not altered, so long as moisture cannot enter.

FUSION. A satisfactory vessel for the fusion can be constructed of ordinary 1- or 1¼-inch iron pipe, 6 to 8 inches long, closed with a cap at the lower end. It is desirable, although not essential, to have on hand for closing the upper end (Note 9) a cap with a hole bored through, big enough to take the thermometer and its protecting tube. This tube should be of copper (Note 10), at least 3 inches longer than the pipe, and, of course, closed at the lower end. In an asbestos board, about 6 inches square, drill a hole in which the pipe fits snugly. Support the pipe by an iron clamp (Castaloy should be avoided, since it may melt at these temperatures), so that the asbestos board is held in place by the clamp jaws (Note 11).

Fuse a mixture of 0.2 to 0.3 mole each of sodium hydroxide and potassium hydroxide in the open pipe, heating with a Fischer or Meker burner (Notes 12 and 13) (*Caution*) to a dull red heat (Note 14), until spattering ceases. Let cool to about 175° (Note 15), and adjust the flame properly to maintain at this temperature. In the meantime, prepare the sodamide for the tube by first transferring solid and liquid to a wide vessel (crystallizing dish, preferably. *Caution:* no flames near), then decanting the petroleum ether, and pressing out the sodamide quickly on thick absorbing paper so as to break up any lumps. Transfer it rapidly but cautiously to the caustic melt (Note 16), and add the dry potassium phenylglycinate, a little at a time down the center of the pipe (Note 17) with occasional stirring, taking care not to spread the melt on the upper, colder part of the tube.

After all is added, put on the cap, and gradually raise the temperature to about 200° in 5 to 10 minutes. Stir frequently. Maintain at 200° to 220° for about 5 minutes, and then slowly raise the temperature to about 300°. If the temperature starts to rise rapidly, immediately remove the burner. Sometimes the temperature spontaneously mounts rapidly to about 300°. Maintain at 290° to 300° for about 5 minutes. Take about 0.5 hour for bringing the temperature from 175° to 300°. Cool to room temperature.

Dissolve the contents of the melt in 0.5 to 1 liter of water in a 2-liter or larger vessel, taking care to keep the mixture cool. Without needless delay precipitate indigo by air oxidation, preferably by a stream of fine air bubbles, until precipitation of indigo is complete (Note 18). Collect by suction filtration or by centrifuging, and wash a few times with water. Add hydrochloric acid (1 or 2 N) in excess, warm for some

time in order to dissolve iron compounds completely, and collect the solid by suction filtration. Wash until free of hydrochloric acid. Determine the weight of crude dry indigo.

Purify the indigo by dissolving it at 45° in a closed vessel in about 100 ml. of water containing a weight of sodium hydrosulfite and sodium hydroxide, each equal to the weight of crude indigo. Filter the warm solution quickly with minimum contact with air. Expose the filtrate to air as before. Collect the indigo by suction filtration, wash, dry thoroughly, and calculate the percentage yield, after thorough drying (Note 19).

Notes

1. It is essential that apparatus and reactants be dry. The yield is higher if the salt is finely divided.

2. In lieu of a standard taper joint, use preferably a carefully bored rubber stopper, so that water, which condenses on the outside of the condenser, cannot enter the flask.

3. Calcium chloride cannot be used, for it absorbs ammonia and expands.

4. Add the Dry Ice first and then the isopropyl ether cautiously until the condenser is partly filled. If it is too full, the liquid may be thrown out by the escaping gas.

5. Handle the sodium with paper, and place it on a large piece of paper, so as to catch all scraps of sodium oxide and metallic sodium. Do not allow these to touch other objects, such as desk top, floor, or clothing. Woolen and leather goods are rapidly destroyed by sodium hydroxide. Put all scraps into alcohol, and *not into sinks.*

6. This catalyzes the reaction between sodium and ammonia. The reaction is said by some to be hastened by a small amount of water. Addition of some sodium peroxide has been recommended.

7. The coating of ice becomes reasonably transparent if a little glycerol is rubbed on the outside.

8. Arrange this so that any liquid, if it does form, cannot flow back into the flask.

9. Yields of indigo are low if the alkali fusion is carried out in contact with air. This can be diminished if the operation is carried out in a deep vessel. A small opening is also helpful. A deep vessel has the additional advantage that spattering is less. Usually it is necessary to solder on the lower cap with silver solder.

10. Glass is rapidly attacked by the hot molten alkali.

11. The asbestos board serves to protect the hand from the heat of the flame during the time of stirring.

12. Both hydroxides are used, to obtain a lower-melting mixture. An excess is needed, so that the fusion mass will be liquid throughout, at the reaction temperature.

13. *Caution:* The molten caustic is *very destructive.* Do not let it come in contact with skin, clothing, or desk top. Wear goggles and rubber gloves, and protect the desk below with an asbestos pad. Any alkali spilled should be neutralized *immediately.*

14. The light should not be bright in the room; otherwise, it is impossible to tell when a dull red heat is reached.

15. Test by slowly lowering the thermometer, incased in the copper tubing.

16. Since the sodamide reacts rapidly with the moisture of the air, undue exposure must be avoided. The oily film need not be entirely removed, and this protects the sodamide somewhat.

17. Ammonia is evolved at this point, sometimes with spattering. The finely divided solid may blow out of the pipe.

18. If the reaction mixture stands in concentrated aqueous alkali for some time, the yield is low.

19. The yield of reprecipitated indigo is 50%.

Questions

1. Why should all reactants be anhydrous?
2. What causes the color of solutions of sodium in ammonia?
3. Why is petroleum ether added?
4. What are the advantages and disadvantages of the other methods of preparing sodamide?
5. Explain how the melting point of the alkali mixture varies from those of the pure bases.
6. What is the approximate temperature corresponding to a dull red heat?
7. What is the purpose of heating the alkali to such a high temperature?
8. What is the purpose of the sodamide in the melt?
9. How much excess hydrosulfite is used in the purification process?
10. Why is sodium hydroxide added in the purification?
11. Write the equation for the reaction of indigo with sodium hydrosulfite and sodium hydroxide.
12. What are the main impurities in the crude and final products?
13. State the steps that were taken to remove them.

Experiment 44–3   Properties of Pyrrole

A PREPARATION OF PYRROLE. *1.* Heat (*Hood*) about 1 g. of raw bone chips strongly in a test tube, and test the outgoing vapors for pyrrole (see B).

2. Heat (*Hood*) about ¼ g. of ammonium mucate or ammonium saccharate (Note 1) with about ½ ml. of glycerol in a test tube, and test the outgoing vapors for pyrrole.

3. Heat (*Hood*) about ¼ g. of succinimide and ¼ g. of zinc dust strongly in a test tube, and test the outgoing vapors for pyrrole.

B REACTIONS OF PYRROLE. *1. Pine-splint test.* Moisten a pine splint in concentrated hydrochloric acid, and hold it in the vapor of pyrrole (Note 2). Repeat with aniline, pyridine, quinoline, and indole, heating if necessary. If no test is given, dip the splint in a dilute (1 or 2%) solution of the compound in alcohol.

2. Ehrlich test. To dilute solutions of pyrrole and indole add a few drops of a 5% solution of *p*-dimethylaminobenzaldehyde in dilute

hydrochloric acid.   Test also with a solution of *p*-nitrobenzaldehyde in dilute hydrochloric acid (Note 3).

3. Isatin test.   Make a very dilute solution (0.001 to 0.01%) of isatin in about 10 ml. of concentrated sulfuric acid.   To one portion add a very small amount of pyrrole (a drop of a solution of pyrrole in some solvent), and shake 5 to 10 ml. of commercial benzene with the other portion (Notes 4 and 5).   Let the two liquids stand for several minutes.

4. Polymerization.   Add 3 drops of pyrrole to 1 ml. of concentrated hydrochloric acid.   After it has stood 5 minutes, make the mixture basic by addition of concentrated ammonium hydroxide (Note 6).

5. Bromination.   Dilute 1 or 2 drops of pyrrole with carbon tetrachloride, and add a solution of bromine in carbon tetrachloride, drop by drop.

6. Iodination.   Repeat Experiment 19–6G, but replacing ethyl alcohol with pyrrole (Note 7).

7. Diazonium coupling.   Add pyrrole to a weakly acidic solution of benzenediazonium chloride (Notes 8, 9, and 10).

Notes

1. Ammonium mucate may be prepared by dissolving mucic acid in an excess of ammonium hydroxide and evaporating on a water bath.

2. Do not permit hydrochloric acid to get into the stock bottle of pyrrole. Since pyrrole is expensive, use only small amounts in these experiments.

3. Pyrroles couple in the *alpha* position with *p*-dimethylaminobenzaldehyde to give red pyrrolenine compounds.   The red color is due to the possibility of resonance in the positive ion.
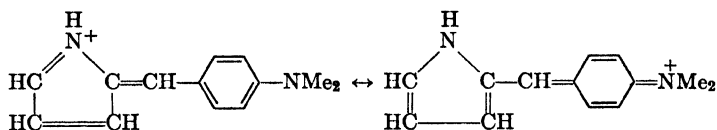
4. Commercial benzene contains thiophene, which gives an intensely blue color with isatin.   This is due to the formation of indophenine.
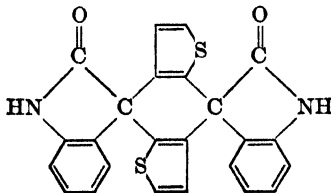
5. If a blue color is not obtained with pyrrole repeat, but use a solution of isatin in dilute sulfuric acid.

6. The polymer is believed to have the following structure.
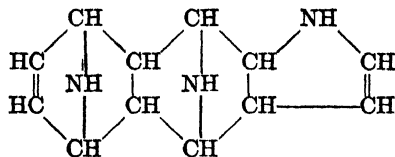
7. Tetraiodopyrrole is the antiseptic iodol. It is much used in place of iodoform. The iodination reaction of pyrrole forms the basis for a quantitative determination of pyrrole.

8. See Chapter 34 for the preparation of a diazonium salt.

9. The solution may be buffered with sodium acetate. The amine should be completely diazotized before the buffering agent is added.

10. In the weakly acid solution coupling takes place in one *alpha* position. In an alkaline solution both *alpha* positions couple if unoccupied by substituents.

Questions

1. How does ammonium mucate decompose to give pyrrole? Equation.
2. What role does glycerol play in the decomposition of ammonium mucate?
3. Write the equation for the action of zinc dust on succinimide.
4. How does the intense color with Ehrlich's reagent arise?
5. Write the structures of indole, indoxyl, and isatin.
6. To what are the colors in the isatin tests due?
7. Show a probable mechanism for the polymerization of pyrrole.
8. Why is ammonium hydroxide added after the polymer formation?
9. Write equations for the bromination and iodination of pyrrole.
10. How can one distinguish the pyrrole iodination from an iodoform test?
11. How does pyrrole compare with phenol in regard to ease of substitution?
12. Why should the amine be completely diazotized before the buffering agent is added? (See Note 8.)

Chapter 45

CHROMATOGRAPHY

Chromatography is the process of separating substances by adsorbing them differentially on a solid adsorbent. Usually the substances are separated by means of a continuous flow of solvent downward through a vertical tube, packed with the adsorbent. The passage of the solution usually is aided by suction or by pressure. Under ideal conditions the adsorbates (the adsorbed substances) initially are in a narrow zone at the top of the column. In the case of colored substances the zone is clearly visible.

The substances are separated by the passage of more solvent down the column. The adsorbates move down the column at different rates and slowly become separated from each other in the form of zones or bands. This operation is called **development of the chromatogram.** When the substances are colored, the development of the bands and their progress down the tube can be followed easily. Finally the colored zones are separated from each other by colorless zones.

The pure substances are obtained by: (1) separately collecting the portions of the solution as the bands leave the column, or (2) cutting the column, after extrusion from the tube, into sections so that each section contains a single band, and eluting the desired substance from the section with a solvent of high eluting power. The various portions of the filtrate obtained in the first method are said to constitute a **liquid chromatogram.**

Colorless substances that fluoresce in ultraviolet light can be followed in their progress down the tube by illuminating in the dark with ultraviolet light. Other colorless substances may be detected by analysis of the liquid after passage through the column or by extruding the column and then either applying a suitable color-developing reagent to the column in a long narrow strip or cutting the column into sections and analyzing the sections.

Thus the operations of chromatography, in the order in which they are carried out, involve: (1) preparation of solution and column, (2) introduction of the solution, (3) development, (4) removal of the column, (5) sectioning of the column, and (6) elution.

45.11 Applications of Chromatography. Chromatography is useful in: (1) separating the components of mixtures, (2) purifying substances, (3) establishing the homogeneity or nonhomogeneity of materials, (4) identifying substances by means of mixed chromatograms with known substances, in a manner analogous to mixed melting points, and (5) increasing the concentrations of dissolved substances, especially in very dilute solutions. In many separations chromatography is superior to any other method because: (1) Many substances having very similar properties can be separated from each other; (2) the method is satisfactory with microquantities; and (3) is mild and reversible.

Chromatography is an extremely useful tool in the separation and isolation of natural pigments and can be carried out easily, owing to visibility of the bands. It has been applied successfully to the carotenoids, anthocyanins, chlorophylls, blood pigments, porphyrins, bile pigments, and others. It has been extended also to colorless compounds, and sometimes is called **colorless chromatography** in this connection. Ion exchange and partition chromatography are newer techniques.

45.12 Choice of Adsorbent and Solvent. The strength of adsorption can be regulated by the choice of adsorbent and of solvent. Any solid substance may be considered as a potential adsorbent, but it must be compatible with the adsorbate. Solids vary in their ability to adsorb other substances. In Table 45–1, first column, are listed some common adsorbents in the approximate order of decreasing adsorbing power. The order is not fixed, since the absorbing power of a substance varies with the manner of preparation and often is greater, the smaller the particle size; also, the order is different with different adsorbates.

The eluting powers of solvents vary. Saturated aliphatic hydrocarbons are poor eluters. The presence of functional groups increases eluting power, and this usually is greater, the greater the polarity of the functional group. In Table 45–1, second column, are listed some common solvents in the approximate order of eluting power. The order is not fixed but varies with adsorbent and adsorbate. When water is the solvent, the eluting power may be altered by changing the pH.

Usually a different solvent is used for each of the three operations, namely, initial adsorption, development, and elution. In order to obtain a narrow zone initially, a solvent of low eluting power, often ligroin, is used. Moreover the solution should not be too dilute. In order to develop the chromatogram satisfactorily, a solvent of higher eluting power is needed. There must be a careful balance between eluting power of the solvent and adsorbing power of the adsorbent. If the substances are too strongly adsorbed, they remain at the top of the column, and, if too weakly adsorbed, they rapidly move down the

TABLE 45-1

GENERAL RELATIONSHIPS IN CHROMATOGRAPHY *

Solids in Decreasing Order of Adsorption Strength	Solvents in Decreasing Order of Eluting Power †	Radicals in Decreasing Order of Effect on Adsorption Affinity †
Fuller's earth	Acids (organic)	COOH
Alumina (activated) §	Pyridine	OH
Silicic acid (activated) §	Water	
Calcium hydroxide ‖		$N{=}N$
Magnesia	Alcohol	COR
Magnesium carbonate	Acetone	NH_2
Calcium carbonate	Esters	NO_2
Sodium carbonate		COOR
Talc	Ether	
		Cl
Sucrose ¶	Carbon disulfide	
Starch	Chloroform	C_6H_5
Diatomaceous earth	Carbon tetrachloride	
	Toluene	
	Benzene	
	Ligroin	

* These relationships are only approximate.

† These relationships are entirely different on nonpolar adsorbents such as Norite.

§ Activity increases on ignition, decreases on exposure to moist air.

‖ Recommended for separating carotenoids. Different samples vary widely in activity.

¶ Recommended for separating the chlorophylls.

column and out at the bottom before separation has been effected. In order to elute the bands, a solvent of still higher eluting power is needed. *The adsorbent, the solvent, and the adsorbate must be compatible.*

45.13   Adsorption Affinity.   The adsorption affinities of various adsorbates for a given adsorbent differ.   Saturated aliphatic hydrocarbons are the least strongly adsorbed and thus have the lowest adsorption affinity.   The important factors that increase adsorption affinity are polar functional groups, length of conjugated systems, and *cis* configuration (relative to *trans*).   Increase in molecular weight may also be a factor, but a minor one.   In Table 45-1, third column, are listed a number of functional groups in approximate order of effect on adsorption.   The order is not fixed but varies with compound and adsorbent.

45.14 Preparation of the Column. For obtaining a successful chromatogram the adsorbent must be packed evenly in the tube, and, when it is a mixture, as for example when diatomaceous earth has been added to increase permeability, it must be uniform in composition. If channels or cracks are present, or if the components are not thoroughly mixed, the passage of the solution will not be uniform, thus causing such distortions of the chromatogram that later it may be impossible to separate the layers. However, even in the best-packed tubes a phenomenon that may be called "coning" is likely to occur. If a column in which coning has occurred is cut, it may be seen that the pigment near the outer section of the column has moved either farther or less far down the column than that in the middle. Generally the column should be packed with the suction turned on, as in Experiment 45–1. Sometimes the column is formed by suspending the adsorbent in solvent, adding it to the tube, and then drawing the liquid through. This produces a very tightly packed, extremely slowly filtering column and in general is not used.

45.15 Introduction of the Solution and Development. The solution containing the substance should be poured rapidly onto the top of the column so that the entire surface is wetted almost simultaneously. Care should be taken *not to disturb the surface*. Disturbance of the surface may cause unevenness of zones later, probably because the pigments are unevenly distributed in the top layer. Once started, the chromatogram should not become dry on top even momentarily, until development is complete. Whether development should be carried out with the original solvent or with another, a so-called stronger developer, depends on the individual case. In general it may be stated that, if the movement of the zones is very slow, a stronger developer should be used. The most convenient method for automatically and continuously adding developer is to place the liquid in a separatory funnel, close this with the stopper, and suspend the funnel over the column with a ring. When the stopcock is opened, the liquid runs out until the tip of the funnel is covered. When the level of the liquid drops below the tip, air enters, thus allowing some liquid to flow out.

45.16 Removal of the Column and Separation of the Components. After development has been completed, the column is removed from the glass tube by applying pressure with the tamper at the bottom of the column. Removal is facilitated if the bore of the tube is smaller at the bottom than at the top. The column is extruded horizontally, and the separation of the components carried out with a knife or scalpel. This should *not* be done by cutting across the column at the position indicated by the zone. If coning has occurred, the major portion of the zone may be lost if the column is cut in this manner. In

order to cut a column correctly it is sliced at a sharp angle to the long axis by drawing the scalpel toward one's self. The slicing is continued until the entire upper portion has been brought into view. The zone is cut out in like manner. If more than one zone is being investigated, this operation is continued the length of the column.

45.17 Elution. The desired zone, after it has been separated, is broken up with the scalpel, placed in an Erlenmeyer flask, and covered with a solvent of high eluting power (see Table 45–1). After being shaken for several seconds to cause even suspension of the solid, the adsorbent is separated by gentle suction filtration through a sintered glass funnel or a Buechner funnel with several circles of filter paper. The filter cake is washed until the solvent comes through colorless.

45.18 Apparatus. A simple chromatographic tube is shown in Figure 45–1. The tube is improved by the use of standard taper joints. The lower joint should be a male joint. The column can be supported by a circular perforated glass plate which either can rest on the end of the male joint or be fused to it. The tamper is shown in Figure 45–2.
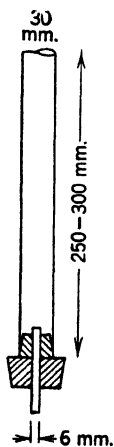
FIG. 45–1
Chromato-
graphic
Tube
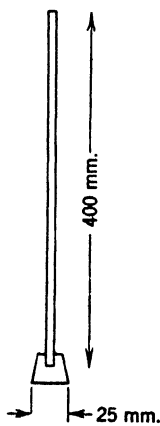
FIG. 45–2 Tamper
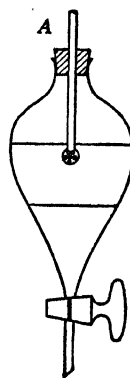
FIG. 45–3 Auto-
matic Washer

Experiment 45–1   Isolation of Lycopene (Notes 1 and 2)

Prepare a chromatographic tube as shown in Figure 45–1 (Note 3). The lower rubber stopper should fit a 500-ml. suction flask. Also prepare a tamper as shown in Figure 45–2, using a cork stopper and a piece of dowel.

Prepare an extract of tomato paste by adding 300 ml. of methanol to the contents of a 6-ounce can in a wide-mouthed screw-capped bottle (Note 4). Shake the whole vigorously for 30 seconds every few minutes for ¼ hour. Then filter with suction on a Buechner funnel, using cloth instead of filter paper. Press, and wring the filter cake dry. Discard the filtrate. Return the filter cake to the bottle, and extract the pigments twice with a mixture of 100 ml. of ligroin (b.p. 60–70°) and 100 ml. of methanol (Note 5) and finally once with a mixture of 180 ml. of ligroin and 20 ml. of methanol, filtering and wringing dry between each extraction. Combine the filtrates in a large separatory funnel which must be free of stopcock grease (Note 6), filtering if not clear. Carefully add ca. 600 ml. of water, and swirl gently, to transfer any pigment from the methanol to the ligroin, taking care to avoid emulsification. Wash the ligroin completely free of methanol with water. Swirl with 600-ml. portions of water (at least seven), or use an automatic washer (Figure 45–3; Note 7), until the initial cloudiness disappears. Dry rapidly in a large Erlenmeyer flask with a suitable neutral drying agent (Note 8). Unless the experiment can be completed without stopping, store the extract in a cold place. It is advantageous to reduce the volume to about 100 ml. by evaporation at room temperature under reduced pressure.

Place the adsorption tube in a vertical position on a 500-ml. suction flask. Tamp a layer of cotton on the bottom of the column, about 5 mm. All subsequent operations should be carried out without delay. Add calcium hydroxide (Note 9) slowly under gentle suction, while tapping the tube all the while. Frequent light tamping aids in preventing cracks. Complete the filling of the tube, leaving the upper 3 to 4 cm. empty. Press the top of the column firmly and evenly with the tamper. Wrap a towel about the tamper, and remove powder from the glass above the column. Finally press the top once more.

Add the extract rapidly so that the entire surface of the column is covered simultaneously, and be careful not to disturb the surface while adding any subsequent liquid. As the last of the extract is drawn into the column, start development with 10% acetone in ligroin (b.p. 60–70°), but do not permit the column to become dry at any time. The main red band of the chromatogram is lycopene. The remaining zones are β-carotene and other carotenoids. Develop until the lycopene is separated from other pigments by white interzones (Note 10). When this stage has been reached, allow the column to become dry, and break the vacuum suddenly (Note 11). Push the column out of the top of the tube (Note 12), make a sketch of the column in your notebook, cut out

the main red zone of lycopene in the manner described in the discussion, and elute with ether.

Evaporate the eluate from a 50-ml. distilling flask, running the solution in from a separatory funnel, and heating with a water bath. Do not permit the bath temperature to rise above 45° (Note 13). Dissolve the dry residue in the minimum amount of benzene at 45°, and transfer with a dropper to a centrifuge tube. Add methanol cautiously with stirring. After crystals form, add more methanol until its volume is three to four times that of the benzene (Note 14). The crystals may be centrifuged, washed with methanol, and recrystallized in the same manner. Collect the crystals on a very small funnel, dry in a vacuum desiccator for an hour, and weigh on an analytical balance (Note 15). Take the melting point in a sealed tube filled with carbon dioxide (Note 16), and seal the rest in a tube filled with carbon dioxide or nitrogen.

Notes

1. Lycopene is an acyclic aliphatic hydrocarbon, $C_{40}H_{56}$, with 11 conjugated and 2 isolated double bonds. It is more strongly adsorbed than the carotenes, also $C_{40}H_{56}$.

2. This experiment may be modified for the isolation of β-carotene ($C_{40}H_{56}$, 11 conjugated double bonds). Two hundred and fifty grams of fresh carrots are extracted as indicated after having been chopped in a meat grinder. The mass should be chopped between extractions. Development should be carried out with pure ligroin or with not more than 1% acetone in ligroin. The main orange layer is β-carotene. Of the three carotenes, α-carotene has the weakest and γ-carotene the strongest adsorption affinity. The *alpha* isomer has 10 conjugated and 1 unconjugated double bond; the *beta*, 11 and 0; and the *gamma*, 11 and 1. There is only an insignificant amount of the *gamma* form in carrots.

3. It is desirable to measure the diameter of the top and bottom of the tube and to place the smaller end at the bottom in case there is a difference. This facilitates the removal of the column later.

4. Tomato paste is about 10% solids. The per cent of lycopene on the dry basis is about 0.2% but varies considerably. A second or even a third extraction with methanol is advantageous, for emulsification later during the washing of the petroleum ether extract with water is not so troublesome, probably because fats are better removed.

5. Mechanical shaking for 15 minutes is advantageous at this point.

6. The development of the column may be affected by the presence of oily impurities.

7. Water enters through the tube *A* (Figure 45-3) which has several openings at the lower end, and which is held in position by an air-tight stopper. Water leaves the separatory funnel through the open stopcock as fast as it enters, and the levels remain constant if no air enters the separatory funnel.

8. A mild alkaline agent is satisfactory, but not an acidic one.

9. A powder funnel is convenient at this stage. The calcium hydroxide should be at least 80–100 mesh. It is advantageous to add one-half part of Celite, to facilitate flow of liquid. It is highly important to mix the two solids thoroughly.

10. The amount of developer cannot be specified because of the difference in the activity of various calcium hydroxide samples.

11. When this is done, a film of air passes between glass and adsorbent, thereby facilitating the removal of the column.

12. If the column cannot be removed easily, invert the tube, and tap it against a folded towel on the table top, or gently tap the outside of the tube.

13. It is advantageous, although not absolutely necessary, to use reduced pressure, to remove the ether at a relatively low temperature. Lycopene is heat-labile. It isomerizes slowly, even at room temperature.

14. Crystals of lycopene formed in this manner are very small but microscopically homogeneous.

15. Usually the weight of lycopene isolated is 10 to 15 mg.

16. The melting point of lycopene or other carotenoid should be taken in a sealed tube filled with carbon dioxide. The sample should be introduced into the melting-point apparatus not more than 20° below the melting point. Melting points: lycopene, 173°; β-carotene, 183°. Absorption spectra maxima, in benzene: lycopene, 522, 487, 455 mμ; and β-carotene, 497.5, 493.5 mμ.

Questions

1. What is the purpose of treating the tomato paste with methanol?
2. Write the structural formulas of lycopene and β-carotene.
3. Why not use 30–60° ligroin initially?
4. Why is the nature of the solvent changed when development is started?
5. Why not use 30–60° ligroin in the development?
6. Why does the presence of some acetone in ligroin aid development of the chromatogram?
7. Why not increase the proportion of acetone to 25 or 50%.
8. Which is more strongly adsorbed, lycopene or β-carotene?
9. How do you account for the difference?
10. Why is the vacuum broken suddenly?
11. Which solvent elutes better: acetone or ether?
12. Why not use acetone for eluting?
13. Is lycopene readily soluble in benzene?
14. Why not use benzene for eluting?
15. Is lycopene readily soluble in methanol?
16. Why is lycopene stored in a sealed tube filled with nitrogen or carbon dioxide?
17. Why is the melting point taken in a sealed tube so filled?
18. Why should the temperature be not more than 20° below the melting point?

Chapter 46

QUALITATIVE ORGANIC ANALYSIS

The purpose of qualitative organic analysis is the identification of organic compounds. This is done by correlating the chemical and physical properties of a given compound with those of a compound of known structure. The analogy between the two compounds is made complete by a comparison of the physical properties of their derivatives.

The chemical properties of the compound depend on the so-called "functional groups" which are present in the molecule. The presence or absence of a particular functional group is deduced from the behavior of the compound with the reagent that reacts specifically with such a group. Although in general this is true, the reactivity of a particular group may be markedly altered by other structural features in a molecule, leading to either diminished or enhanced reactivity.

The physical properties that in general are most used are the melting point and the boiling point. The density, refractive index, specific rotation, and absorption spectrum are less frequently used.

The reliability of the observed chemical and physical properties depends on the purity of the compound. A small amount of impurity may cause misleading results. Purification can be accomplished by employing one or more of the standard methods of purification: namely, crystallization, distillation, sublimation, extraction, and chromatography.

Certain quantitative procedures are of value in identification, for example the determination of the molecular weight and of the percentage composition, which lead directly to the molecular formula. This is of especial value for new compounds. Other useful quantitative determinations are: (1) the neutralization equivalent of an acid or base, (2) saponification equivalent of an ester or amide, (3) unsaturation equivalent as by bromine absorption, and (4) methoxyl value.

Derivatives are necessary in order to distinguish between two or more compounds that react alike. Sometimes a single derivative is sufficient, because it possesses some property that distinguishes it from the derivatives of all similar compounds. In general, however, two derivatives are necessary, and sometimes even three. Solid derivatives are preferred because of ease of determining melting points and are valuable

since, if necessary, they can be identified by means of mixed melting points. The properties most useful in derivatives are the melting point, the neutralization equivalent in the case of acids and bases, and the optical rotation, in the case of a relatively few compounds. Sometimes the boiling point of a derivative is useful.

The following abbreviated scheme of qualitative organic analysis is intended for use in connection with a limited number of organic compounds; these are the hydrocarbons (saturated and unsaturated, acyclic and cyclic) and their derivatives such as halogen compounds, alcohols, phenols, ethers, aldehydes, ketones, carboxylic acids, anhydrides, acid chlorides, esters, amines, amides, nitriles, nitro and azo compounds, mercaptans, sulfides, sulfonic acids, amino acids, and sugars. Salts of organic acids and bases are included. Many classes of organic compounds are not included, for example heterocyclic compounds and compounds containing other elements (phosphorus, arsenic, and the like). It will be necessary for the student to refer to other work when details of procedure are not given in this text or when data on derivatives are desired (Note 1).

The examination of the compound in question should in general follow this order: (1) qualitative tests for the elements, (2) ignition test, (3) solubility tests, (4) tests for functional groups, (5) determination of physical constants, (6) selection of possibilities, (7) preparation of derivatives.

In order to assure familiarity with the various tests, it is well to carry out beforehand tests with known compounds. This applies not only to the tests for the elements and to the ignition tests but also to tests with various reagents.

SECTION 46.1 PRELIMINARY TESTS

46.11 Detection of Nitrogen, Sulfur, and Halogens. DECOMPOSITION WITH SODIUM. Place a piece of clean metallic sodium the size of a small pea in a small test tube (2 or 3 inch) *suspended through a piece of asbestos board.* Add a little of the material (one drop of a liquid or a few fragments of a solid), and heat the tube with a small flame until the sodium melts and the vapors of sodium form a layer about 1 cm. in height. Allow 3 drops of the unknown, if liquid, or an equivalent quantity of fragments of solid to fall at intervals of 1 or 2 seconds directly on the fused sodium without touching the sides of the tube. (*Caution!*) Heat the reaction mixture strongly so as to oxidize most of the residual sodium as well as to remove volatile organic decomposition products (Notes 2 and 3).

Immerse the hot tube in water, with *Caution*, as follows: The tube is merely touched to the surface of 12 ml. of water, in a small beaker, and then raised out of the liquid but held in the beaker in such a manner that the heavy glass of the beaker will be between the tube and the eyes of the operator. Momentary contact with water will cause the hot tube to crack, and traces of unreacted sodium will be destroyed by spontaneous burning without the dangers of a hydrogen explosion. The cooled tube is now tapped against the inner side of the beaker, and the lower cracked part is allowed to drop into the water. The solid particles are broken up with a stirring rod, and the solution is heated to boiling and filtered. The filtrate, which should be colorless, is reserved for the subsequent tests. It is referred to later as the alkaline stock solution (Notes 4 and 5).

NITROGEN TEST. Boil 2 ml. of the alkaline stock solution for 2 minutes with 5 drops of ferrous sulfate and 1 drop of ferric chloride solution. Cool, and acidify carefully with hydrochloric acid. The precipitate of iron hydroxide should dissolve readily; otherwise, the solution should be warmed very gently. A clear yellow solution indicates a negative test. A blue or greenish-blue solution suggests the presence of nitrogen but indicates that the original sodium decomposition may have been poor. A positive test is a precipitate of Prussian blue, which shows up best when collected on filter paper (Note 6). If iodine is present, the filter is washed with acetone or alcohol to dissolve out the iodine.

SULFUR TEST. To 1 ml. of the filtrate made slightly acid with acetic acid add a few drops of lead acetate reagent. A black precipitate of lead sulfide shows the presence of sulfur.

TESTS FOR HALOGENS. *1. General Test.* Acidify 2 ml. of the stock solution with c.p. dilute nitric acid, and boil for 2 or 5 minutes to expel any hydrogen sulfide or hydrogen cyanide, if present; otherwise, the boiling may be omitted. Add a few drops of aqueous silver nitrate. A precipitate denotes the presence of halogens, provided the volatile compounds just mentioned have been expelled completely, and provided also the reagents are free of halogens. For this reason a blank should be run. Also apply the Beilstein copper oxide wire test to the original unknown (see Experiment 16–5A).

2. Test for Iodine. Acidify 2 ml. of the stock solution with dilute c.p. nitric acid, and, after it is free of sulfide and cyanide, add a few drops of 1 N sodium nitrite and 0.5 ml. of carbon tetrachloride. Shake well. A purple color in the carbon tetrachloride layer is due to the presence of iodine. Save the aqueous phase.

3. Test for Bromine. If iodine is present, remove the carbon tetrachloride layer, add a few more drops of acid and of sodium nitrite to

the aqueous phase, and extract several times with carbon tetrachloride until all iodine has been removed.

To detect bromine in the iodine-free solution, which should be slightly acidic, add about 0.5 ml. of carbon tetrachloride and then aqueous potassium permanganate dropwise until a pink color remains. Then add 2 to 4 drops more. Shake for a few minutes. A yellowish-to-brown color in the carbon tetrachloride layer shows the presence of bromine.

4. Test for Chlorine. If bromine is present, remove it by diluting the aqueous phase to 30 ml. and boiling gently for several minutes. If the pink color fades, add more permanganate. Finally reduce excess permanganate and any manganese dioxide by the addition of a few more drops of sodium nitrite and of acid.

Add to the bromine-free solution a few drops of nitric acid and of aqueous silver nitrate. The formation of a white precipitate insoluble in nitric acid shows the presence of chloride ion (Note 7). A faint chloride test may be due to a trace of chloride in either the metallic sodium or the reagents (Note 8).

46.12 Ignition Test. Place about 0.1 g. of the material on platinum foil (Note 9), and heat with a very small flame. The phenomena to be observed are: (1) melting, (2) ignition, (3) character of the flame, (4) residue left after heating to redness, (5) reaction of residue with dilute hydrochloric acid.

DEDUCTIONS. The possibility of making a melting-point determination on the compound can be judged by noting if it melts easily. A flame indicates that the compound is volatile or forms volatile decomposition products when heated. A sooty flame indicates unsaturation or the presence in the molecule of aryl radicals or of alkyl radicals of four or more carbon atoms. A residue indicates the presence of a metal. Insolubility of the residue in hydrochloric acid indicates an insoluble salt or metal.

46.13 Solubility Tests. Determine the approximate solubility of the compound according to the general procedure of Experiment 2–1, in water, ether, dilute (about 1 N) hydrochloric acid (Note 10), dilute (about 1 N) sodium hydroxide, dilute (about 1 N) sodium carbonate, and ice-cold concentrated (or 80%) sulfuric acid. If the compound dissolves in concentrated (or 80%) sulfuric acid, pour the resulting solution at once onto two to four times the amount of finely crushed ice. Note if any oil or solid is thrown down (Note 11).

In case the compound is soluble in water, it will, of course, be soluble also in dilute acids and bases, provided, however, there is no chemical reaction by which a compound insoluble in the aqueous medium has been formed.

DEDUCTIONS. Solubility in water may be the result of a sufficiently high oxygen-to-carbon or nitrogen-to-carbon ratio in the molecule of the compound, or to the fact that it is a salt. The simple alcohols, aldehydes, ketones, acids, ethers, esters, anhydrides, amines, and amides up to and including the compounds containing four carbon atoms per molecule are water-soluble. Those having more than five carbon atoms per molecule are only slightly soluble in water (less than 5%). Of halogen-containing compounds, alkyl chlorides (and fluorides) are lighter than water. Most other halogen compounds are heavier.

Insolubility in ether may be due to a high melting point, to a high oxygen-to-carbon ratio, to a high nitrogen-to-carbon ratio, or to a salt structure.

Solubility of a water-insoluble compound in dilute hydrochloric acid indicates a base. Solubility in aqueous sodium hydroxide indicates a strong, weak, or very weak acid, and, in aqueous sodium carbonate, a carboxylic or stronger acid, or a nitrophenol.

Solubility in concentrated sulfuric acid may result from the presence in the molecule of oxygen, nitrogen, a multiple carbon-to-carbon bond, or an easily sulfonated aromatic ring. In the case of oxygen and nitrogen compounds, the reactions are essentially those of salt formation (oxonium and ammonium types, respectively). On dilution with water a second phase may appear. This may be the original compound if it is a very weak base, or it may be the sulfate if the original compound is an amine.

If the compound is unsaturated, it may dissolve in sulfuric acid as a result of an addition reaction, leading to the formation of an alkyl acid sulfate (alkyl sulfuric acid). This remains in solution on dilution with water. However, another reaction may take place, namely, polymerization. This may be misleading, since the polymer probably will be insoluble.

If the compound is easily sulfonated, it will dissolve in both the concentrated sulfuric acid and the diluted acid. A phenol is suggested.

Notes

1. Refer to *Qualitative Organic Analysis*, 2d ed., by Oliver Kamm, John Wiley & Sons, 1932; *Identification of Organic Compounds*, 3d ed., by R. L. Shriner and R. C. Fuson, John Wiley & Sons, 1948; *Identification of Pure Organic Compounds*, by S. P. Mulliken, John Wiley & Sons, 1914–1921; and *Identification of Pure Organic Compounds*, by E. H. Huntress and S. P. Mulliken, John Wiley & Sons, 1941.

2. *Caution:* Since the fusion point of glass is lowered when in contact with metallic sodium, a small flame is desirable.

3. The procedure is modified for volatile compounds, as follows: The sample is placed in the tube first and the sodium is suspended 1 or 2 inches above it on a plug of glass wool. The sodium is heated first with the tube in a slanting position.

4. If the filtrate is dark colored, decomposition was incomplete, probably because the temperature was not high enough.

5. Organic compounds undergo destructive reduction when heated with metallic sodium, yielding various products, such as sodium carbonate, sodium hydroxide, sodium cyanide, sodium sulfide, sodium chloride, sodium bromide, sodium iodide, carbon, methane. In the resulting mixture nitrogen is identified as cyanide ion, sulfur as sulfide ion, and the halogens as halide ions. Sometimes, when reduction is incomplete, nitrogen and sulfur if present together, may appear as sodium thiocyanate. This may be detected by the red color given on the addition of ferric ion in weakly acidic solution.

6. Prussian blue may become soluble (be peptized) if the acid concentration is too high. The color due to ferric ion can be discharged by the addition of a few drops of a solution containing fluoride ion.

7. Silver nitrite may precipitate in case much nitrite is present.

8. A blank test should be run.

9. The platinum foil, about 1 cm. square, should be attached to a glass rod by a short piece of platinum wire, 22 or 24 B. and S. gage, which is welded to the foil.

10. When attempt is made to dissolve an organic acid or base by a neutralization reaction, care must be taken that the concentration of the reagent is not too high; otherwise, the salt may precipitate, owing to the common ion effect. Indeed, a solid acid or base may not even react, owing to protection by a layer of solid salt. The effect is more important with compounds of low solubility in water, usually those of high molecular weight.

11. The diluted acid (75 to 85%) has some advantages over the concentrated acid: (1) Sulfonation is largely eliminated; (2) polymerization is very much less in the short time allowed for the test. However, higher alcohols (about C_9 and higher) are not soluble, and the rate of addition to olefins is likewise much less. If the compound seems to undergo change with the concentrated acid, it would be well to repeat with the less concentrated acid.

SECTION 46.2   DEDUCTIONS FROM PRELIMINARY TESTS

Merely as a result of tests to this point, it is possible to draw deductions in regard to the nature of the compound, as the following outline shows:

I. No residue on ignition:
    A. Negative test for the elements:
        1. Soluble in water:
            (a) Soluble in ether: Lower alcohol, ether, aldehyde, ketone, acid, ester, anhydride (slowly soluble in water); medium glycol, hydroxy acid, dibasic acid (medium m.p.).
            (b) Insoluble in ether: Ethylene glycol; high-melting dibasic acid; hydroxy acid, polyhydric alcohol, sugar.
        2. Insoluble in water:
            (a) Soluble in ether: Hydrocarbon, higher oxygenated compound.

        (b) Insoluble in ether: Compound of high melting point: starch, etc.

        (c) Soluble in dilute NaOH: Acid, phenol, enol.

        (d) Soluble in concentrated H_2SO_4: Unsaturated compound, or one containing oxygen.

B. Positive test for nitrogen:

   1. Soluble in water:

        (a) Soluble in ether: Lower amine, amide, nitrile; medium amino acid, amino alcohol, diamine.

        (b) Insoluble in ether: Low amino acid, amino alcohol, diamine; salt of amine with carboxylic acid.

   2. Insoluble in water: Nitro, azo, azoxy or hydrazo compound; higher amine, amide, etc.

        (a) Soluble in dilute HCl: Aromatic amine; higher aliphatic amine.

        (b) Soluble in dilute NaOH: Imide, oxime, nitroparaffin; acid or phenol containing nitrogen.

C. Positive test for sulfur:

   1. Soluble in water: Alkyl acid sulfate; sulfonic acid, lower sulfoxide.

   2. Insoluble in water: Dialkyl sulfate; alkyl sulfonate; mercaptan, sulfide, disulfide, sulfoxide, sulfone.

D. Positive test for halogen:

   1. Soluble in water: Oxygen-containing compound, as halogenated lower alcohol or acid; low acid chloride (react.).

   2. Insoluble in water: Halogenated hydrocarbon, as alkyl halide, aryl halide. halogenated higher alcohol, acid, etc.

        (a) Soluble in dilute NaOH: Halogenated phenol, higher acid.

        (b) Soluble in concentrated H_2SO_4: Compound containing halogen and oxygen.

E. Positive tests for nitrogen and sulfur:

   1. Soluble in water: Amine sulfate; sulfonated amine; ammonium or substituted ammonium salt of sulfonic acid, etc.

   2. Insoluble in water: Amine sulfate; sulfonated amine; sulfonamide; many others.

F. Positive tests for nitrogen and halogen:

   1. Soluble in water:

        (a) Soluble in ether: Lower halogenated amine, nitrile, amide.

        (b) Insoluble in ether: Amine hydrohalide.

   2. Insoluble in water: Halogenated amine, amide, etc.

G. Positive tests for nitrogen, sulfur, and halogen:

   1. Soluble in water: Sulfonated compound, salt of complex amine, etc.

   2. Insoluble in water: Many combinations.

II. Residue on ignition:

  A. Negative tests for elements (on original): Salt of carboxylic acid or of phenol with a metal.

  B. Positive test for nitrogen (on original): Salt of amide, imide, amino acid, nitro acid, etc., with a metal.

  C. Positive test for sulfur: Salt of mercaptan, sulfinic acid, sulfonic acid, alkyl hydrogen sulfate, etc., with a metal.

  D. Positive test for halogen: Salt of halogenated acid or phenol with a metal.

SECTION 46.3   TESTS FOR FUNCTIONAL GROUPS

46.31   Halogen, Nitrogen, and Sulfur Absent. Test first for acidity. Use the ferric hydroxamate test first for anhydrides and then for esters. The test can be extended to acids or to alcohols by converting these to esters. Before the saponification test for ester is carried out, tests should be made first for acid radicals (including anhydrides), next for the oxo group (in aldehydes and ketones), and then for the hydroxyl group (in alcohols and phenols). These tests must precede the test for esters (by saponification), because base may be consumed by the following: (1) acids and anhydrides, (2) aldehydes which undergo dismutation, (3) β–keto esters like acetoacetic ester which may undergo scission, (4) phenols (especially nitrophenols) which may form salts. Finally, test for the ether linkage. A substance not reacting as any of the foregoing is a hydrocarbon.

ACIDS. Test the aqueous solution with an indicator. If this turns litmus red, the compound may be an acid, an anhydride, or a reactive ester. Determine the neutralization equivalent by titration with a standard base. Save the solution for the preparation of a derivative, according to (2) below. If an ester, very little base should be required. However, some esters, ethyl oxalate for example, titrate like acids, owing to rapid hydrolysis. Anhydrides may be detected by the ferric hydroxamate test (Experiment 24–3D).

The most useful solid derivatives (Note 1) are: (1) an amide and (2) a substituted phenacyl ester. (1) Convert the acid to the acid chloride which then is allowed to react with ammonia or, better yet, with aniline or p-toluidine (Experiment 23–2). Anhydrides react with aniline or p-toluidine without heating (Experiment 24–3). (2) To the neutral solution of the salt, made by neutralizing the aqueous solution of 1 g. acid with sodium hydroxide and evaporated to a small volume, add ethanol and then 0.8 to 1 g. of a substituted phenacyl bromide, such as p-phenylphenacyl bromide. Reflux the mixture for at least 1 hour (dibasic acids, 2 hours). When reaction is over, collect the product by filtration, and recrystallize it from ethanol, or from ethanol–water mixture.

If a salt of an acid is indicated, add dilute sulfuric acid in excess to an aqueous solution of the salt and extract the aqueous solution with ether. On evaporation of the ether the acid is left behind. Tests may be made on the residue. If the acid is only slightly soluble in water it may precipitate out when sulfuric acid is added. If it is very soluble in water, continuous ether extraction may be necessary.

ALDEHYDES AND KETONES. These may be detected by the use of 2,4-dinitrophenylhydrazine in the form of a saturated alcoholic solution

containing 2% of concentrated hydrochloric acid. They react readily to form solid 2,4-dinitrophenylhydrazones when heated. Derivatives may be made with this solution, or by the procedure of Experiment 25–5G (Note 2). Oxo compounds may be detected and identified also by conversion to semicarbazones by means of semicarbazide, or to other hydrazones by substituted phenylhydrazines.

Aldehydes differ from ketones in that they color fuchsine–bisulfite solution (Schiff's reagent) and reduce Fehling's solution, Benedict's solution, and ammoniacal silver solution (Experiment 25–5). However, hydroxy ketones (for example ketoses) act like aldehydes toward these oxidizing agents.

ALCOHOLS. Alcohols may be detected by the readiness with which they react with acetyl chloride (Experiment 23–2) or with acetic anhydride (Experiment 24–3) to produce esters. Also they evolve hydrogen on the addition of sodium (Experiment 19–6). However, many other compounds, as for example acids, ketones, and esters, evolve hydrogen also.

The three classes of alcohols may be distinguished from each other as follows: Tertiary alcohols react rapidly with concentrated hydrochloric acid to form insoluble liquid chlorides; secondary, with 3 volumes of hydrochloric acid–zinc chloride reagent (Note 3) in 5 minutes at 28° to form insoluble chlorides; primary alcohols react with neither.

The most useful solid derivative for an alcohol is the 3,5-dinitrobenzoate obtained by means of the acid chloride of 3,5-dinitrobenzoic acid (Note 4). However, tertiary alcohols yield the corresponding chloride. Sometimes in the presence of a tertiary base (pyridine) the ester is obtained from a tertiary alcohol. This modification gives better yields with any alcohol.

PHENOLS. Phenols are very slightly soluble in water and in aqueous sodium bicarbonate and readily soluble in dilute (about 1 N) sodium hydroxide (Note 5). Their aqueous solutions usually precipitate brominated phenols on the addition of bromine water (Experiment 35–4).

One of the most useful of derivatives is the aryloxyacetic acid obtained by the action of sodium chloroacetate on the sodium salt of the phenol (Note 6).

ESTERS. They may be detected by the ferric hydroxamate test (Experiment 21–5C). They react slowly when heated under reflux with aqueous sodium hydroxide. In case the alcohol is a lower alcohol, a single phase finally results. When boiled in a test tube with 3 to 5 volumes of sulfuric acid, 75 to 85% (Experiment 21–5), an ester yields an acidic distillate if the organic acid is volatile.

If an ester is suspected, determine the saponification equivalent (Experiment 21–4), and identify the acid and alcohol constituents (Note 7).

ETHERS. Ethers are cleaved by refluxing with concentrated hydriodic acid for 1 to 2 hours or, better, by heating in a sealed tube with a saturated solution of hydrogen bromide in glacial acetic acid. Alkyl halides are formed which can be identified. A mixed alkyl–aryl ether yields a phenol and an alkyl halide. Diphenyl ether is not changed by this treatment.

HYDROCARBONS. Olefinic and acetylenic hydrocarbons rapidly decolorize a solution of bromine in carbon tetrachloride and rapidly reduce aqueous permanganate (Experiments 14–4 and 15–2). Aromatic hydrocarbons can be distinguished from aliphatic with chloroform and aluminum chloride (Experiment 29–3).

Saturated aliphatic hydrocarbons are identified by physical constants. Olefins may be converted to addition compounds with halogens or nitrosyl chloride, but, in general, the products are liquids. Permanganate oxidation yields acids, which can be identified. Alkynes likewise may be converted to addition compounds or oxidized. They may be hydrated to ketones. Derivatives of aromatic hydrocarbons may be obtained by sulfonation, nitration, oxidation, or condensation with phthalic anhydride to a benzoylbenzoic acid (Experiment 36–2), or by chlorosulfonation to a sulfonyl chloride, and ammonolysis of this to a sulfonamide (Experiment 31–4).

46.32 Halogen Present. The type of halogen compound is indicated by adding 1 to 2 drops of a liquid, or equivalent amount of a solid, to about 2 ml. of alcoholic silver nitrate and allowing to stand for about ½ hour. Instantaneous precipitation indicates ionic halogen. Acyl halides react very rapidly. Tertiary halides react readily; secondary slower; primary still slower. Iodides are more reactive than bromides, and these more so than chlorides (Experiment 16–5). Aromatic compounds are unreactive except when the halogen is on a side chain. Acyl halides may be detected by the ferric hydroxamate test (Experiment 21–5C).

Solid derivatives may be obtained from primary and secondary alkyl halides by heating with an aqueous alcoholic solution of the sodium salt of p-bromobenzenesulfon-p-anisidide, or by conversion to an alkyl mercuric halide (Experiment 18–3). Solid derivatives of the aryl halides are not prepared by the use of any single reagent. In some cases, nitration to a mono or a dinitro compound is useful; in others, condensation with phthalic anhydride to a halogenated anthraquinone is best (Experiments 36–2 and 38–3).

POSITIVE HALOGEN. Many halogen compounds liberate iodine when hydriodic acid is added. In such a compound the halogen atom may be attached to an oxygen atom, as in a hypochlorite; to a nitrogen atom; or to a carbon atom *alpha* to a keto group, as in chloroacetone or in bromoacetoacetic ester.

46.33   Nitrogen Present.   Test first with litmus. A basic reaction may indicate an amine or an amine salt of a weak organic acid (amino acid, nitrophenol, and so on). An acid reaction may indicate a nitro acid, a nitrophenol, or an amine salt of a strong acid.

AMINES (or salts of amines). The three classes of amines, that is, primary, secondary, and tertiary, may be distinguished by means of benzenesulfonyl chloride (or *p*-toluenesulfonyl chloride) and aqueous sodium hydroxide (Note 8; Experiment 33–3).

Primary aliphatic amines may be distinguished from primary aromatic amines by sodium nitrite and hydrochloric acid at 0° to 5°. Nitrogen is evolved with aliphatic amines (Experiment 26–2). However, primary amides evolve nitrogen also, but the acid concentration must be high. Also addition of the resulting solution to alkaline aqueous β-naphthol gives an intense color in the case of aromatic amines.

Derivatives of primary and secondary amines may be prepared by the action of acid chlorides or anhydrides. Among the most useful reagents are benzenesulfonyl chloride or *p*-toluenesulfonyl chloride, as in the Hinsberg test. The derivatives usually are solid. Moreover, these reagents are of value also in classifying the amine. Other reagents useful for making derivatives are acetic anhydride and benzoyl chloride, the latter with aqueous base, as in the Schotten–Baumann reaction.

Salts of acids, for example the picrates and nitrobarbiturates, are of value as derivatives of primary, secondary, and tertiary amines.

If a salt of an amine is suspected, the amine (provided it does not contain an acid group) may be recovered by adding an excess of aqueous sodium hydroxide and extracting with ether. Lower diamines, however, are very soluble in water and are not easily extracted. Evaporation of the ether solution leaves the amine, provided it is not volatile (the lower aliphatic amines are volatile). However, for making derivatives under alkaline conditions the free amine need not be isolated.

AMIDES AND NITRILES. These may be detected by (*a*) the evolution of a volatile acid when boiled with fairly concentrated (60 to 80%) sulfuric acid, or (*b*) the evolution of a volatile base (ammonia or an amine) when boiled with concentrated aqueous sodium hydroxide (Experiments 27–4 and 28–2). In the first case the amine is present as the sulfate; in the second case the acid is present as the sodium salt (Note 9). In *a* the acid, if nonvolatile, sometimes crystallizes out

on cooling. Sometimes the sulfate of the amine separates. In *b* the base, if nonvolatile, usually separates as an oil when hot. The identification is made complete by identifying the acid and the base. Amides may be detected by the ferric hydroxamate test (Experiment 21–5C).

Nitriles can be reduced to primary amines (Experiment 28–2). These can be identified as previously described.

Nitro and Nitroso Compounds. A general test for the nitro or nitroso group consists in reducing it under neutral conditions to the hydroxylamine compound, which reduces ammoniacal silver ion (see Experiment 32–3). Derivatives are obtained by reduction to the amine, and conversion of this to a solid.

Azo and Azoxy Compounds. These become colorless when reduced by tin and hydrochloric acid, or by stannous chloride and hydrochloric acid in alcohol. Each molecule gives rise to 2 molecules of amine.

46.34 Sulfur Present. Test with litmus. An acid reaction may indicate a sulfonic acid, an alkyl acid sulfate, a salt of one of these with an amine, or a sulfonyl chloride.

Sulfonic Acids. These usually are water-soluble. Also, their salts usually are soluble. Acids or salts may be converted into acid chlorides by heating with phosphorus pentachloride. These then are converted to sulfonamides with ammonium hydroxide, or ammonium carbonate (Experiment 31–5).

Sulfonamides. The presence of sulfur and nitrogen in the compound and a negative test for sulfate ion strongly suggests a sulfonamide. Generally, these are not very soluble in water. Solubility in dilute (not over 1 N) sodium hydroxide (Note 5) suggests RSO_2NH_2 or RSO_2NHR, whereas insolubility suggests RSO_2NR_2. The first two types may be converted to derivatives by the reaction of an alkyl iodide (or bromide) on the sodium salt in aqueous alcoholic solution.

Mercaptans. The sulfhydryl group is detected by the reduction of iodine, and also by the formation of an insoluble salt with mercuric ion. The disulfide, formed when the mercaptan is oxidized, may serve as a derivative.

Sulfides. Derivatives may be prepared by oxidation to the sulfones.

46.35 Residue on Ignition. To obtain the free acid, add an excess of dilute sulfuric acid to the original substance, and extract with ether (Note 10). Recover the organic acid by evaporation of the ether. The acid is then subjected to all the tests, as if it were the original compound. The cation may be determined by the methods of qualitative inorganic analysis.

Dibasic acids, hydroxy acids, and amino acids are difficult to extract with ether. In some cases, for example malic acid, this can be done by

a long continuous process of extraction. Some acids, namely, oxalic, tartaric acids, and many so-called sugar acids, cannot be extracted this way.

Notes

1. Tables of derivatives suitable for the identification of many classes of organic compounds can be found in other works. See Note 1, Section 46.1. Details for the preparation of derivatives are given.

2. The amount of dinitrophenylhydrazine is sufficient to prepare plenty of the hydrazone for identification purposes. Since it is an expensive chemical, no more than the amount specified should be taken.

3. This reagent to be effective should be made from c.p. concentrated hydrochloric acid (sp. gr. 1.18) and anhydrous zinc chloride (1 mole per mole of HCl) by dissolving the solid in the acid, while cooling to 0°. If the acid is below strength, the reagent is not satisfactory. On standing it loses hydrogen chloride. Therefore, it should not be used if too old.

4. This acid chloride hydrolyzes so readily and deteriorates so rapidly when stored that it is not profitable to try to keep it. Instead, the acid chloride is made as needed from the acid, 0.5 g., and phosphorus pentachloride, 1 g., by warming gently in a test tube. After the first vigorous reaction is over, the mixture is boiled gently for about 5 minutes and then allowed to solidify on a watch glass. It is then pressed out thoroughly on porous tile, to remove adhering liquid.

5. See Note 10, Section 46.1.

6. The reagent is prepared by neutralizing chloroacetic acid with aqueous sodium hydroxide. The amount taken should be in excess (10 or 20%) over the amount of phenol.

7. After saponification, the alcohol, if volatile, can be distilled out. Derivatives of the acid are made directly from the potassium salt, following dilution of the reaction mixture with 8 to 10 ml. of 50% ethyl alcohol and careful neutralization with a strong acid, preferably sulfuric acid. Any potassium sulfate that separates should be removed.

8. The Hinsberg test is especially valuable when the amine to be tested is insoluble or only slightly soluble in water. The reaction should be continued until all the sulfonyl chloride has disappeared, and the solution should be decidedly basic at that time, but the time should not be extended too long. In addition to the initial observation of solubility, the behavior towards hydrochloric acid is important. The aqueous and the organic phase, if there are two phases, should be separated from each other first and the acid added to each phase. When the original amine is water-soluble, the method is useful in detecting a primary or secondary amine, provided the sulfonyl derivative is insoluble or only slightly soluble in water. The Hinsberg test is of no value with a soluble tertiary amine.

9. Of course, if the compound is a salt, either an acid or a base will be liberated on the addition of the corresponding reagent. However, this will occur in the cold.

10. Since ether is more soluble in aqueous acids than in water, the excess of sulfuric acid should not be too great.

Questions

1. Write the equations for the formation of Prussian blue in the nitrogen test.
2. How does potassium fluoride discharge the color of ferric ion?

3. Why must hydrogen sulfide and hydrogen cyanide be expelled before a test is made for halide ion?

4. Write the equations for the reactions of iodide and bromide ions with different amounts of chlorine.

5. What types of compounds will leave on ignition residues that are insoluble in hydrochloric acid?

6. State the behavior of the following compounds, slightly soluble in water, with cold aqueous (about 1 N) hydrochloric acid: acetanilide, anthranilic acid, benzoic acid, benzenesulfonamide, n-butyl acetate, sec-butyl acetate, n-capraldoxime, p-cresol, isopropyl ether, naphthalene, α-naphthol, α-naphthylamine, nitrobenzene, o-nitrophenol, 1-pentanol, n-octyl alcohol, p-tolunitrile.

7. Ditto, but with cold aqueous (about 1 N) sodium hydroxide.

8. Ditto, but with cold aqueous (about 1 N) sodium carbonate.

9. Ditto, but with cold 80% sulfuric acid.

10. Write equations for any reaction in 6, 7, 8, and 9.

11. What additional reaction may take place if the mixture with 80% sulfuric acid is heated?

12. Write balanced equations for the following reactions:

(*a*) Acet-p-toluidide from acetic acid and (?).

(*b*) p-Phenylphenacyl acetate from acetic acid and (?).

(*c*) Propionaldehyde and 2,4-dinitrophenylhydrazine.

(*d*) Acetophenone and 2,4-dinitrophenylhydrazine.

(*e*) Preparation of 3,5-dinitrobenzoyl chloride.

(*f*) 3,5-Dinitrobenzoyl chloride and n-butyl alcohol.

(*g*) Bromine (1, 2, and 3 moles) and o-cresol (1 mole).

(*h*) Sodium chloroacetate and sodium phenoxide.

(*i*) n-Butyl acetate and potassium hydroxide (in alcohol).

(*j*) Ethyl n-butyl ether and concentrated hydriodic acid (distilled).

(*k*) Ethyl n-butyl ether and hydrogen bromide in acetic acid.

(*l*) 2-Pentene (excess) and aqueous potassium permanganate.

(*m*) 1-Pentene and aqueous potassium permanganate (excess).

(*n*) 1-Pentyne and aqueous potassium permanganate (excess).

(*o*) 1-Pentyne (excess), ammoniacal silver nitrate.

(*p*) 1-Pentyne (excess), aqueous mercuric sulfate and sulfuric acid.

(*q*) Preparation of nitrosyl chloride.

(*r*) Nitrosyl chloride and 3-hexene.

(*s*) Toluene and mixture of anhydrous nitric and sulfuric acids (in excess).

(*t*) Toluene and hot aqueous alkaline permanganate.

(*u*) Ethyl bromide, potassium hydroxide, and p-bromobenzenesulfon-p-anisidide.

(*v*) Potassium phthalimide and benzyl bromide.

(*w*) Ethyl mercuric iodide from an alkyl halide.

(*x*) 2-Chloroanthraquinone from an aryl halide.

(*y*) N-Chloroacetanilide and hydriodic acid.

(*aa*) Benzene sulfonyl chloride, sodium hydroxide (aqueous), and toluene.

(*ab*) Benzene sulfonyl chloride, sodium hydroxide (aqueous), and phenol.

(*ac*) Benzene sulfonyl chloride, sodium hydroxide (aqueous), and p-toluidine.

(*ad*) Benzene sulfonyl chloride, sodium hydroxide (aqueous), and N-methyl-p-toluidine.

(*ae*) Benzene sulfonyl chloride, sodium hydroxide (aqueous), and N,N-dimethyl-p-toluidine.

(*af*) Dimethylaniline and methyl iodide.

(*ag*) Sodium nitrite, hydrochloric acid (aqueous), and *n*-butyl alcohol.

(*ah*) Sodium nitrite, hydrochloric acid (aqueous), and *n*-butyl ether.

(*ai*) Sodium nitrite, hydrochloric acid (aqueous), and *n*-butylamine.

(*aj*) Sodium nitrite, hydrochloric acid (aqueous), and acetamide.

(*ak*) Sodium nitrite, hydrochloric acid (aqueous), and urea.

(*al*) Sodium nitrite, hydrochloric acid (aqueous), and di-*n*-butylamine.

(*am*) Sodium nitrite, hydrochloric acid (aqueous), and aniline.

(*an*) Sodium nitrite, hydrochloric acid (aqueous), and *N*,*N*-dimethylaniline.

(*ao*) Sodium nitrite, hydrochloric acid (aqueous), and *o*-cresol.

(*ap*) Sodium nitrite, hydrochloric acid (aqueous), and ethyl benzoate.

(*aq*) Aniline and acetic anhydride.

(*ar*) Aniline and acetyl chloride.

(*as*) Aniline and *p*-nitrobenzoyl chloride.

(*at*) Propionamide and sodium hydroxide (aqueous, hot).

(*au*) Propionitrile and sodium hydroxide (aqueous, hot).

(*av*) Nitrobenzene, zinc, and ammonium chloride.

(*aw*) Nitrobenzene, stannous chloride, and hydrochloric acid.

(*ax*) Azobenzene, stannous chloride, and hydrochloric acid.

(*ay*) Azoxybenzene, stannous chloride, and hydrochloric acid.

(*az*) Iodine and thiophenol.

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